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PURPOSES

The main purpose of the Physiological Reviews is to furnish a means whereby those interested in the physiological sciences may keep in touch with contemporary research. The literature, as every worker knows, is so extensive and scattered that even the specialist may fail to maintain contact with the advance along different lines of his subject. The obvious method of meeting such a situation is to provide articles from time to time in which the more recent literature is compared and summarized. The abstract journals render valuable assistance by condensing and classifying the literature of individual papers, but their function does not extend to a comparative analysis of results and methods. Publications such as the Ergebnisse der Physiologie, the Harvey Lectures, etc., that attempt this latter task, have been so helpful as to encourage the belief that a further enlargement of such agencies will be welcomed by all workers. It is proposed, therefore, to establish a journal in which there will be published a series of short but comprehensive articles dealing with the recent literature in Physiology, using this term in a broad sense to include Bio-chemistry, Bio-physics, Experimental Pharmacology and Experimental Pathology.

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THE GASTRIC JUICE IN PANCREATIC DIABETES

M. E. STEINBERG

From the Department of Physiology of the University of Chicago and the University of Oregon Medical School

Received for publication March 8, 1921

Rabens (10) in his studies on blood transfusion from normal into diabetic dogs, has found, incidentally, that on the same diet the diabetic dogs eliminated in the urine only from about one-seventh to one-tenth of the chlorides found in the urine of normal dogs.

Verhaegen (13) reports three diabetic patients, two examined by himself and one by Kultz, whose gastric juice did not contain any hydrochloric acid.

Great hunger and appetite and increased capacity to digest meat have been observed in dogs with pancreatic diabetes.

To throw more light upon the above-mentioned observations, and to search for a possible relation between the secretion of the pancreas and that of the stomach, the study of the gastric juice in experimental pancreatic diabetes was undertaken.

EXPERIMENTAL METHODS

Operation: The abdominal incision for the Pavlov stomach pouch was made to the left of the linea alba and the opening was brought out 2 cm. to the left of the umbilicus. The pancreas was removed at one step, the abdominal incision being made to the right side of the linea alba.

The gastric juice was collected by inserting a rubber tube, perforated at several places, into the pouch. A glass tube was inserted into the external orifice of the rubber tube so as to insure the drainage of the gastric juice to the outside, some distance from the abdominal wall. A small bottle, into which the glass

tube drained the gastric juice, was fastened to the trunk of the dog by means of straps.

In order to avoid all inhibitory influences, the animals were never kept in frames. In the active secretion period they were constantly watched to prevent any attempt of an animal to turn on its back and thus spill the gastric secretion.

The acidity of the gastric juice was determined by titrating with $\frac{1}{10}$ N NaOH, using dimethyl-amino-azobenzol and phenolphthalein as indicators.

The chlorides were determined according to the Volhard-Harvey method. However, instead of 2 cc. $\frac{1}{2}$ N ammonium thiocyanate being equal to 1 cc. of N AgCl, 4 cc. of $\frac{1}{4}$ ammonium thiocyanate solution were made equal to 1 cc. N AgCl, thus insuring more accurate results. In titrating according to the Volhard-Harvey method the first change of color throughout the mixture must be taken as an end point. If the solution which is being titrated is left to stand for a very short period the thiocyanate will have a solvent effect upon the silver chloride, and the light brown color of the end point will disappear, and thus further titration will give inaccurate results.

The pepsin activity of the gastric juice was determined by the Mett's egg albumin tube method, modified by Carlson, and calculated according to the Shutz law.

RESULTS

In order to demonstrate the character of the gastric juice before and after total pancreatectomy with respect to the secretion curve and the chemistry of the gastric juice, a few tables are inserted.

TABLE 1

The average hourly secretion of gastric juice

HOURS	DOG 7		DOG 9	
	Normal*	Diabetic†	Normal‡	Diabetic§
	Average diet 292 grams cooked meat	Average diet 260 grams cooked meat	Average diet 270 grams raw meat	Average diet 125 grams raw meat
1	11.8	3.7	9.0	1.8
2	8.8	7.4	8.1	3.5
3	7.4	10.9	6.9	5.8
4		11.8	6.7	5.5
5		11.1	6.0	8.1
6		10.5	6.3	6.9
7		4.3	6.6	3.4
8		3.2	4.4	4.7
9		5.3	4.0	5.6
10		5.4		4.9
11				6.8
12				1.0

* Average of 12 experiments.
† Average of 7 experiments.
‡ Average of 4 experiments.
§ Average of 5 experiments.

The secretion curve. From table 1 it is evident that on a diet of meat the normal animal secretes the highest quantity of gastric juice in the first 2 hours. The curve of secretion then gradually declines, but the secretion period lasts from 4 to 8 hours. This curve, as obtained by us on normal dogs having a meat diet, is evidently the same as the curve obtained by Pavlov under similar conditions. Dogs 7 and 9, before total pancreatectomy, yield the highest quantity of gastric juice in the first hour and the yield then declines with some fluctuations, but the active secretion period lasts over 9 hours.

After total pancreatectomy dog 7 secreted in the first 2 hours less than he did in the normal condition; the secretion rising in the 3rd, 4th, 5th and 6th hours; the greatest being obtained in the 4th hour, followed by decrease in the 7th hour and another increase in the following hours. The secretion period lasted over 11 hours. Dog 9, after total pancreatectomy, has secreted in the first hour less than in any other single hour of the active secretion period. The curve rose in the 3rd, 4th, 5th and 6th hours, the peak was reached in the 5th hour; followed by a sudden drop in the 7th hour and another rise in the following hours. The active secretion period lasted more than 12 hours. Thus the secretion curves in both dogs after total pancreatectomy are apparently alike, and quite different from the normal secretion curve.

The lengthening of the secretion curve in diabetic dogs is evidently due to the lasting spasm of the pylorus on the duodenal side. Pavlov (9) observed that the passage of acid solution out of the stomach is remarkably slower in the case of dogs with pancreatic fistula. Tobler (12) and Lang (7) have shown that acid protein on the duodenal side checks gastric evacuation. Hedblom's (6) experiments show that potato with 0.25 per cent acid passes out of the stomach more slowly than normal potato, and faster than potato of 1 per cent acidity. Later, Boldyreff (1) showed that fluid of 0.5 per cent acidity passes out quickly from the stomach into the duodenum and the acidity of the fluid remaining in the stomach is reduced to about 0.15 per cent. When the pancreatic ducts are ligated, the acid fluid remains in the stomach for a longer period, and the acidity is reduced to only about 0.40 per cent. Cannon's results are to the effect that the acidity on the duodenal side closes the pylorus. These observations lend support to our contention that the lengthening of the secretion curve of gastric juice after total pancreatectomy is due to the absence of the external secretion of the pancreas, which according to Boldyreff is the chief factor in neutralizing the acid contents of the stomach and duodenum. With the absence

of the pancreatic juice, the pyloric sphincter on the duodenal side is thrown into a lasting spasm, retaining the food in the stomach. The longer the food remains in the stomach, the more the secretagogues are formed, and therefore the greater is the secretion of gastric juice. It would seem, therefore, that we have an adaptation by which the food is subjected to pepsin-hydrochloric acid digestion for a longer period than under the normal conditions.

Is there an absence of psychic secretion in pancreatic diabetes? The quantity of gastric juice which a dog yields in the first 2 hours of the active secretion period is equal to one-half of the total amount of that of the whole secretion period (3). The great quantity of secretion obtained in the first 2 hours is explained by the factor of psychic secretion, which is added to the secretion brought about by the action of the secretagogues.

In the diabetic dogs (table 1) the secretion in the first 2 hours is less than that in the normal condition.

In view of the polyphagia present in pancreatic diabetes the question naturally arises: "Is the polyphagia due to hunger or appetite?" According to Luckhart's (8) observations, one of the factors of polyphagia is hunger. The hunger contractions persist after the removal of the pancreas and become more intense with the progress of the disease. As is evident in table 1, concerned with secretion after total pancreatectomy, the first 2 hours of secretion are scanty. The above considerations would suggest that these hunger contractions are not a factor in the production of secretion during the first hours in the normal animal, and that the psychic factor of secretion is absent or impaired after pancreatectomy.

The development of gastritis after total pancreatectomy in dogs with Pavlov stomach pouches. After total pancreatectomy all the dogs developed symptoms of acute gastritis on the 2nd or 3rd day after the operation. They were constantly retching and vomiting. Dog 2 and dog 3 died on the 3rd day after the operation. The post mortem revealed a highly hemorrhagic condition of the stomach and duodenal mucosa. Dogs 7 and 9 also developed symptoms of gastritis. Dog 7 lived 8 days after pancreatectomy and suddenly died. The stomach mucosa showed a highly hemorrhagic condition. Dog 9 was retching and vomiting after the operation for 2 days, but then the symptoms disappeared. This condition of gastritis has not been mentioned, nor apparently ever noticed after total pancreatectomy.

The acidity of the gastric juice after total pancreatectomy is not changed to any considerable degree. Table 2 indicates that after total pancreatectomy the free acidity of the gastric juice in dog 2 was 0.3646 which is about the same as the average acidity of the animal in the normal condition. Dog 3 gave a free acidity of 0.2918 in the single experiment obtained, which is somewhat lower than the average acidity of the same dog in the normal condition. Dog 7 before pancreatectomy gave a free acidity of 0.4224, while after pancreatectomy the average free acidity was brought up to 0.4403. Dog 9 showed a free acidity of 0.4146 before total pancreatectomy and 0.3104 after the pancreas was removed. As indicated by table 2, the percentage of chlorides of the gastric juice before and after pancreatectomy is about the same. The above

TABLE 2

Average acidities. Pepsin concentration and chlorides before and after pancreatectomy

NUMBER OF DOG	FREE ACID		TOTAL ACID		PEPSIN		CHLORIDES	
	Normal	Diabetic	Normal	Diabetic	Normal	Diabetic	Normal	Diabetic
2	0.3630	0.3646	0.4199	0.4010	3.13	6.25	0.50	0.45
3	0.3927	0.2918	0.4320	0.3646	2.31	36.0	0.48	0.46
7*	0.4274	0.4403	0.4585	0.4762	1.51	3.98	0.49	0.49
9†	0.4146	0.3104	0.4527	0.4242	5.55	10.78	0.51	0.46

* Average of twenty-two experiments in the normal dog and thirty-three in the diabetic dog.

† Average of twenty-seven experiments in the normal dog and twenty-two in the diabetic dog.

considerations clearly indicate that there is not any obvious or constant difference between the acidity of the gastric juice in the normal and in the diabetic conditions.

The pepsin concentration of the gastric juice is increased after total pancreatectomy. Table 2 indicates that dog 2 gave an average of 3.13 mm. of digestion in the normal condition; while after pancreatectomy the single experiment gave a peptic concentration of 6.25 mm. Dog 3 gave an average of 2.31 mm. digestion before pancreas was removed, while after pancreatectomy the single experiment shows 36 mm. digestion. Dog 7 gave an average 1.51 mm. of digestion in the normal condition, while after pancreatectomy the pepsin concentration increased to 3.98 mm. Dog 9 gave an average of 5.55 mm. digestion in the normal condition; after pancreatectomy the average pepsin concen-

tration reached 10.78 mm. Thus, there is conclusive evidence that the pepsin concentration of the gastric juice after total pancreatectomy has been increased.

GENERAL CONSIDERATION OF THE ACIDS, CHLORIDES AND PEPSIN OF THE GASTRIC JUICE

The data accumulated in the examination of the gastric juice in the normal animal warrant some remarks in regard to the acidity, chlorides and pepsin concentration.

The free acidity of the gastric juice according to most observers fluctuates between 0.4 per cent and 0.5 per cent. Our data accumulated in the examination of many samples from various dogs, confirm the above

TABLE 3

Showing the relation between rate of secretion and acidity

NUMBER OF DOG	DIET	NUMBER OF EXPERIMENTS	NUMBER OF SAMPLES EXAMINED	AVERAGE QUANTITY PER HOUR	FREE ACIDITY	TOTAL ACIDITY
				cc.		
2	Meat and bread	12	23	2.0	0.2239	0.2792
2	Meat and bread	7	17	3.5	0.3630	0.4199
3	Meat and bread	9	17	2.1	0.1443	0.2974
3	Meat	12	23	4.3	0.3927	0.4320
4	Meat and bread	3	7	1.1	0.0876	0.1699
9	Meat	12	28	9.8	0.4274	0.4585
8	Meat	10	20	19.9	0.4486	0.4822
9	Meat	4	23	8.8	0.4146	0.4527
13	Meat	1	8	8.8	0.4272	0.4905

view. The low acidities obtained in the examination of the gastric juice are evidently due to the slow rate of secretion. If the rate of secretion is low the contact of the acid secretion with the alkaline mucus is more prolonged and the acidity is reduced, due to the neutralizing and diluting factor of the mucus. Table 3 shows that the slow rate of secretion gives low acidity. When the rate of secretion increased due to a change of diet, the acidity of the gastric juice made a striking increase.

The chlorides of the gastric juice have been examined in a number of samples collected from different dogs. Before examination the juice was put through cotton or gauze eliminating the particles of mucus. Tables 2, 4 and 5 indicate a striking uniformity of the chlorides. The chlorides are generally in direct proportion to the acids

when the acids are high. When the acids are low they have a relatively high chloride content. If we assume that the mucus which is mixed with the gastric juice is low in chlorides, the corresponding high chlorides of the gastric juice with low acidities are probably due to the strongly neutralizing effect of the mucus. Our observation on the uniformity of chlorides in the gastric juice confirms the work of Roseman (11).

TABLE 4

Showing relation of pepsin concentration to acidity and chlorides

NUMBER OF DOG	NUMBER OF SAMPLES EXAMINED	FREE ACIDITY	TOTAL ACIDITY	PEPSIN	CHLORIDES
7	7	0.4688	0.4981	3.22	0.52
7	7	0.4591	0.4866	3.00	0.51
7	5	0.4503	0.4849	4.00	0.48
7	9	0.4433	0.4527	4.73	0.48
7	10	0.3728	0.4284	4.97	0.47
9	5	0.4388	0.4594	4.63	0.52
9	4	0.4078	0.4557	5.09	0.51
9	7	0.3948	0.4388	5.91	0.51
9	12	0.1854	20.704	18.7	0.43
9	1	0.0456	0.0912	31.36	0.46

TABLE 5

Continuous secretion of dog 9

HOURS	QUANTITY	FREE ACID	TOTAL ACID	PEPSIN	CHLORIDES
Normal					
	cc.				
9 p.m.–9 am.	20.0	0.0456	0.0912	31.36	0.46
9 a.m.–1 p.m.	5.6	0	0.0549		0.46
Pancreas removed					
8:15 p.m.– 6:30 a.m.	12.0	0.1732	0.2644	16.00	
7:40 p.m.– 7:30 a.m.	18.0	0.1732	0.2827	7.29	
3:30 p.m.– 8:00 a.m.	15.0	0.1732	0.2644		0.39
9:30 p.m.– 5:00 a.m.	12.0	0.2827	0.3281	16.00	0.39
10:10 p.m.– 8:45 a.m.	7.0	0.1185	0.2371	21.16	0.42
10:00 p.m.– 9:00 a.m.	9.0	0.1459	0.2188	34.81	0.46
	9.0	0.2280	0.3646	16.00	0.46
10:00 a.m.– 1:35 a.m.	3.0	0.2188	0.2918	13.69	
1:35 p.m.– 6:35 p.m.	5.0	0.1641	0.2280	22.09	
6:30 p.m.–11:00 p.m.	6.0	0.1641	0.1732	15.21	
11:00 p.m.– 9:00 a.m.	8.0	0.1276	0.2097	16.81	

The continuous secretion is high in pepsin but low in acid. Table 5 gives the continuous secretion of dog 9 before and after pancreatectomy. The gastric juice is low in acid, but high in pepsin. Our findings are in accord with Carlson's observations on continuous secretion in man.

The gastric juice collected during the active secretion period does not show any direct proportion between the acidity and pepsin concentration as noticed by Edkins and Brinkman (2). On the contrary, there is some evidence that gastric juice low in acidity is higher in pepsin as is indicated in tables 4 and 5.

The flocculent, ropy mass, separated from the gastric juice is high in pepsin, but very low in acid. Samples of gastric juice, containing mucus were allowed to stand for a period of from 24 to 48 hours. At the bottom of the test tube a flocculent, ropy mass is then generally found. The examination of this ropy mass proved to be two to four times as high in pepsin as the gastric juice of high acidity which was collected during the active secretion period.

CONCLUSIONS

The secretion of the gastric juice after total pancreatectomy in dogs with Pavlov stomach pouches, is different from the one obtained under normal conditions:

1. The quantity of the first 2 hours is less than that in the normal dogs, indicating the possible disturbance of the mechanism concerned in psychic secretion; the quantity secreted in the 3d, 4th, 5th, and 6th hours of the active secretion period is greater than in the normal curve; the active secretion period is prolonged, lasting twelve or more hours.
2. The total quantity of gastric juice secreted on the same diet has been more than doubled;
3. The pepsin concentration of the gastric juice is greatly increased;
4. The acidity of the gastric juice in pancreatic diabetes does not essentially differ from the normal.

The hyper-secretion of gastric juice, the increase in pepsin concentration, and the longer retention of the food in the stomach, point to an adaptation to prolong and augment the pepsin-hydrochloric acid digestion after total pancreatectomy.

A typical severe gastritis, with constant retching, and vomiting has been observed after total pancreatectomy on dogs with Pavlov stomach pouches.

The free acidity of the normal gastric juice during the active secretion period does not fluctuate much, being between 0.3630 and 0.4146, and the total acidity between 0.4199 and 0.4527. This confirms the work of Pavlov, Carlson, Boldyreff and others.

The chlorides of the gastric juice are uniform, thus confirming the work of Roseman.

Continuous secretion is low in acid but high in pepsin, which confirms the work of Carlson on human gastric juice.

The thick flocculent mucus separated from the gastric juice is high in pepsin, but very low in acid.

I wish to express my thanks to Dr. J. J. Moorhead for his generous help in some of the operations. I am deeply indebted to Doctor Carlson who suggested this problem.

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STUDIES OF THE THYROID APPARATUS

II. The Changes in the Amount of Intestine-Contracting Substances of the Thyroid of the Albino Rat According to Age

F. S. HAMMETT and K. TOKUDA

From The Wistar Institute of Anatomy and Biology, Philadelphia

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It is a well-known fact that aqueous, saline and other extracts of the thyroid gland of various animals cause contraction of the isolated intestinal segment from laboratory animals. Nevertheless since this property is exhibited by extracts of other tissues, such as thymus, spleen, brain, kidney, liver, pancreas, parathyroid, intestinal mucosa and musculature, heart, striated muscle, etc., as Wieland (1), Köhler (2), Fawcett and his collaborators (3), Stern and Rothlin (4), Collip (5) and others have shown, the production of the substances causing the contraction can not be considered as a specific function of any particular tissue. Indeed it is becoming increasingly evident that there are substances elaborated by, or contained in, many tissues of the body which exhibit a common type of effect on the blood pressure, gastric secretion, heart-beat and other physiological processes, and that this general type of reaction must be distinguished from the specific action of extracts of special glands, as Clark (6) has recently emphasized. Attention should be called to the fact that this similarity of type of reaction production by extracts from such obviously functionally diverse organs indicates an underlying fundamental similarity in metabolic procedure of the various tissues and organs of the body as a whole, upon which has been superimposed, through some process of evolution or development, the more prominent physiological function commonly attributed to the particular organ in question.

It is not the purpose of this report to consider the probable nature of the active substances in the extracts, since we have but little if any actual information with regard to this point. Rather our purpose is to present as briefly as possible the changes in the amounts of the

intestine-contracting substances of the thyroid of the a'bino rat according to age, as measured by the reaction induced in isolated duodenal segments of the rat by extracts of this gland.

The isolated duodenal segment of the adult, unexcited, male albino rat was chosen as the test organ for this investigation because of its qualitative and quantitative reliability for comparative studies of this

TABLE 1

The age and sex distribution of the animals the thyroid extracts of which were tested, together with the averages of the intestine-contracting power of the extracts according to the individual age groups

MALES				FEMALES			
(1) Age	(2) Number of tests	(3) Number of rats	(4) Contraction in terms of M/10 Na_2CO_3	(5) Age	(6) Number of tests	(7) Number of rats	(8) Contraction in terms of M/10 Na_2CO_3
days			*per cent*	*days*			*per cent*
New-born	3	15	73.8	New-born	4	31	86.5
10–11	3	9	41.0	10–11	2	10	64.0
15	3	6	47.2	14–15	2	6	92.9
20	3	6	56.8	21–22	2	4	72.2
25	3	6	43.4	25	2	3	111.6
30	3	6	83.9	30	2	3	45.0
40	3	3	41.3	39	2	2	52.9
50	3	3	63.0	50–52	3	3	83.3
60	3	3	70.5	54–55	3	3	63.9
70	4	4	75.9	60	2	2	86.1
79–80	3	3	167.5	70	2	2	72.1
90	2	2	119.8	75	2	2	72.1
100	1	1	121.4	81–83	3	3	105.0
125	3	3	138.6	90	3	3	99.5
150	3	3	228.8	100	3	3	101.7
200	3	3	101.7	125	1	1	95.0
460	1	1	38.1	150	4	4	164.6
500	2	2	59.2	300	4	4	38.6
520	1	1	68.4				

type, as was shown by Hatai and Hammett (7) and Hammett (8). The method of standardization of such a segment has been described in an earlier paper (8) and needs no elaboration.

The extracts, the relative strength of which was tested, were prepared from the thyroid glands of albino rats of ages ranging from newborn to 500 days. All the animals used were healthy and from the standard stock of The Wistar Institute colony. Values were obtained

for both males and females. The thyroid was removed from the animal, under deep ether anesthesia, was weighed and ground in a small mortar with fifty times its weight of fine dry sand to which was added during the grinding that amount of Tyrode's solution (without sugar) which would suffice to make the concentration of the thyroid in the final solution equivalent to 0.25 per cent. Thus in all cases equal

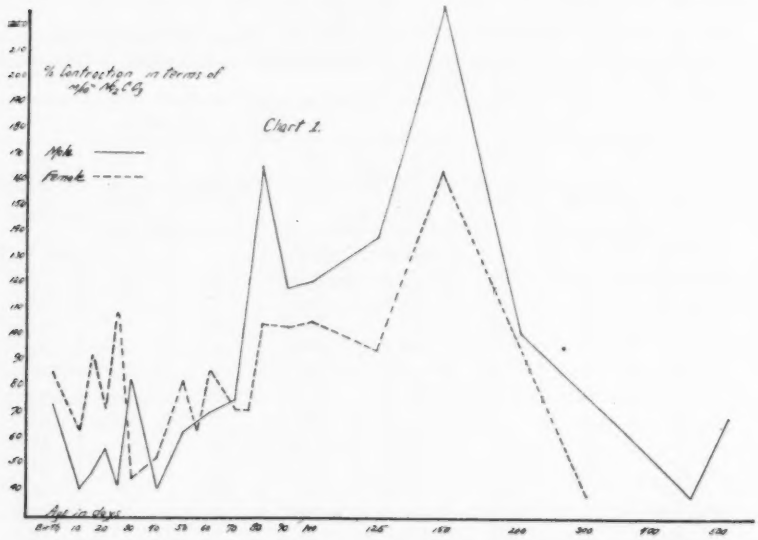

Chart showing the changes in the intestine-contracting power of equivalent amounts of thyroid extracts from male and female albino rats according to age.

amounts of extract from each and all glands were representative of equal unit weights of fresh thyroid tissue. The segments were standardized with 0.25 cc. of M/10 Na_2CO_3 and the shortening induced by 1 cc. of the thyroid extract was compared therewith and expressed as the per cent contraction in terms of M/10 Na_2CO_3.

In all a total of 93 tests was made on 163 animals. The details of the age and sex distribution are given in table 1. The figures in columns 4 and 8 are the average values obtained in the individual age groups studied. These values have been plotted in chart 1. It should be obvious that the size of the thyroid in the very young rats necessitated the use of glands from several animals for each test of the earlier ages.

An inspection of the chart reveals several interesting features. Foremost among these, for purposes of validating the investigation as a whole, is the quite general coincidence of the graphs for the two sexes with regard to the type of change occurring with age. This demonstrates that apparently no marked qualitative sex differences occur, which indicates that the function of these intestine-contracting substances, if they have a function, subserves the same ends in both the male and the female albino. The fact that the course of the curve for the females, while similar to that of the males, precedes by a few days the changes occurring in the graph of the males falls in rather nicely with the observations reported by Donaldson (9) that certain other physiological changes in the female albino rat, such as the opening of the eyes and the onset of puberty, usually occur slightly before they take place in the males, and supports the idea that we are here dealing with an expression, indirect it is true, of a fundamental uniform difference in the development of the two sexes.

If we assume that the variations in the intestine-contracting ability of the thyroid extracts tested are due to variations in the amount of stimulating substances produced per unit weight of thyroid gland, it is at once evident that there are four periods during the active growth of the albino rat when the activity of the thyroid in producing this stimulating complex is noticeably increased: *1*, at birth; *2*, at the period of weaning; *3*, at puberty; and *4*, at the termination of rapid growth, or 150 days. Following each of these periods of higher content of stimulating substances or greater activity in their production, there occurs a marked decrease in the content of the extracts as tested by their action on the isolated intestinal segment. There is the postnatal drop; the post-weaning drop, which is followed by a gradual increase in activity up to the time of the jump to the pubertal high-point; the post-pubertal decrease or, in the females, the post-pubertal plateau; and finally the big decline in activity occurring after the animals have reached full maturity and which is apparently under normal conditions more or less the expression of the activity of the extracts of the thyroid of adult animals. The general trend through all the ups and downs up to the time of this regression is toward an increase in activity. The jog at the time the eyes are opening (about 15 days) may be significant.

The jogs in the curves at weaning and at puberty are similar in their incidence to those observed by Hatai (10) in his study of the refractive index of the blood of the albino rat and when correlated with data that is now accumulating relative to the fatalities following thyreopara-

thyroidectomy at different ages, point strongly to the probability that these two periods, e.g., weaning and puberty, are critical points in development, and points deserving of special investigation. Whether or not they are periods at which the thyroid plays a particular and significant rôle is yet to be determined.

Other studies of evidences of changes in thyroid activity with age have been made. Fenger (11) found that the iodine content of this tissue varied with age, and since he was of the opinion that "the amount of iodine in the thyroid is an indication of the relative activity of the gland" he concluded from his analyses that "there is evidently a gradual rise in activity of the gland in the fetus and this activity is increased shortly after birth, reaching its maximum in the young growing animal." "The iodine content of full-grown animals is very low." This opinion and the findings on which it is based parallel the curves we present. Fenger's studies were made on thyroid glands from beef, sheep and hogs. Moroever Robertson (12) in a brief comparison of the relation of the thyroid weight to body weight of the white mouse, presents figures which show the maximum ratio to exist in animals 70 days of age, while in the adult animals of 210 days the ratio has fallen to that present at 35 days. Since these three separate and distinct lines of investigation give evidence of the same type and direction, it is relatively safe to conclude that a phase of the activity of the thyroid gland, aside from all other factors, changes with the progress of development of the organism.

It is not our intention to give the impression that the tests of the thyroid extracts as carried out in this investigation are to be considered as tests of the specific functional activity of the gland, or as expressing variations in the production of its particular internal secretion which Kendall (13) has isolated and named "thyroxin." In fact the evidence at present available justifies only the opinion that the variations observed are but the particular expressions of general changes in the organism as a whole, in which the thyroid gland, as part of that organism, participates. Nevertheless the possibility must not be overlooked that the thyroid may take a directing or regulating part in these changes and that the variations in its content or production of the intestine-contracting substances as products of its activity may be rough indices of variations in its specific functional activity.

SUMMARY

When the effects on the standardized intestinal segment of equivalent concentrations of extracts of thyroid glands from albino rats of different ages are compared, it is found that certain differences in strength are present according to the age of the animal from which the gland was removed.

Apparently there occurs a heightened content or production of the intestine-contracting substances in the thyroid at birth, at weaning, at puberty, and at the time rapid growth is about completed. Each of these points of increased activity is followed by a period in which the extracts are less active in stimulating the intestinal segment, though the general trend is toward an increase until full maturity, when the activity falls to a fairly uniform low level. This holds for both sexes.

A correlation of these variations with data from other sources leads to the opinion that they are the particular expressions of general changes in the organism in which the thyroid participates.

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STUDIES OF THE THYROID APPARATUS

III. The Action of Thyroxin on the Isolated Intestinal Segment

FREDERICK S. HAMMETT

From The Wistar Institute of Anatomy and Biology, Philadelphia

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In the preceding report it has been shown that extracts of the thyroid gland of albino rats of both sexes at different ages exert a characteristic contracting effect upon the isolated duodenal segment of the same animal.

Since Kendall (1) has shown that the crystalline substance, thyroxin, which he isolated from the thyroid, is an active principle of that gland, in that when it is administered in conditions of hypothyroidism its effect is similar to that of whole gland substance, it seemed worth while to determine whether or not this compound is an active constituent of the thyroid extracts causing the contraction of the isolated intestinal segment. Although the data from other sources indicate that this intestine-contracting ability of the thyroid extracts is not specific but is exhibited by extracts from many other tissues of the body, and although it might appear as if the testing of the possibility of such an effect being produced by thyroxin is superfluous on the basis of the apparent inactivation of the compound when put in alkaline solution, yet since such assumptions of the activity or non-activity of any substance are scientifically dangerous, it was considered that the point should be settled with regard to thyroxin for definiteness if for nothing else.

Since thyroxin is precipitated as the mono-sodium salt from solution in sodium carbonate, if allowed to stand in contact with the air,[1] while it is readily soluble in sodium hydroxide, this latter compound was used in fifteenth molecular concentration, both as the solvent for thyroxin and as the standardizing reagent, instead of the tenth molecular sodium carbonate previously described (2).

One milligram of pure crystalline thyroxin was dissolved in 10 cc. of M/15 NaOH giving a concentration of 0.025 mgm. thyroxin in the 0.25 cc. of solution used for testing and also for standardization. Consecu-

[1] Personal communication from Dr. E. C. Kendall.

tive dilutions with M/15 NaOH were then made which yielded, 5×10^{-3}; 1×10^{-3}; 2×10^{-4}; 4×10^{-5}; 8×10^{-6}; 1.6×10^{-6}; 3.2×10^{-7} and 6.4×10^{-8} mgm. of thyroxin respectively in each 0.25 cc. of solution. A simple calculation will show that the neutralization effect of the thyroxin on the sodium hydroxide, even in the highest concentration, is less than 0.3 per cent, a value extremely small when compared with the limits of accuracy of the method of testing, and which is obviously increasingly diminished with the consecutive dilutions. This wide range of thyroxin concentration was studied because frequently differences in type of physiological reaction to other organic products are observed when

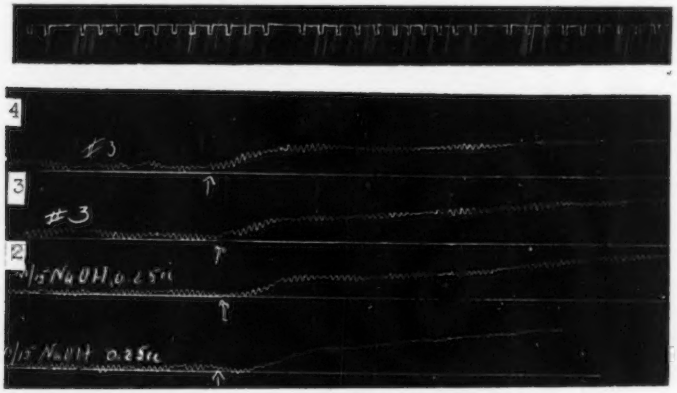

Fig. 1. The effect of 1×10^{-3} mgm. thyroxin on the isolated duodenal segment. The first two tracings are the responses to 0.25 cc. M/15 NaOH as standard; the second two show the response to 0.25 cc. M/15 NaOH plus thyroxin.

different doses are employed. The segments were standardized as described in an earlier report (2), using 0.25 cc. of M/15 NaOH instead of M/10 Na_2CO_3. When the measure of the response of the segment to this amount of NaOH had been obtained the same amount of contracting reagent containing thyroxin of a given concentration was added and its effect compared with the result obtained in standardization.

In no case was there any evidence obtained that thyroxin causes of itself a shortening of the intestinal segment, since in no case did the NaOH solution of thyroxin cause an increase in contraction over that produced by the NaOH itself. The general type of reaction is shown in figure 1.

However, the solutions where thyroxin was present in concentrations of 3.2×10^{-7} and 6.4×10^{-8}, particularly the former, seemed to exert a depressant or retarding effect on the contraction, as is shown in figure 2.

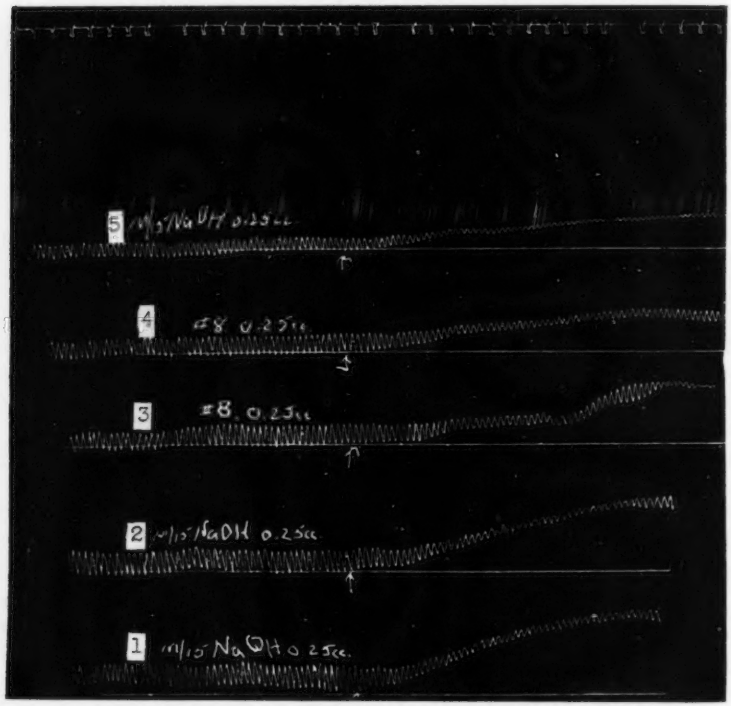

Fig. 2. The effect of 3.2×10^{-7} mgm. thyroxin on the isolated duodenal segment. The first two tracings are the responses to 0.25 cc. M/15 NaOH as standard; the second two show the response to 0.25 cc. M/15 NaOH plus thyroxin; while the fifth tracing is that obtained with 0.25 cc. M/15 NaOH alone.

This amount of thyroxin represents but an extremely small proportion of the iodine present either in normal blood, as determined by Kendall (3), or in the thyroid gland, as reported by Fenger (4), and suggests that the larger proportion of the iodine in the blood or the thyroid gland is not in combination as thyroxin, if this reaction is an expression

of a physiological activity of the compound on the tissue used for testing.

The results do show, however, that thyroxin is not an active constituent of the thyroid extracts, as described in the preceding paper, in causing the characteristic effect on the isolated intestinal segment.

SUMMARY AND CONCLUSION

Solutions of thyroxin in fifteenth molecular sodium hydroxide, in concentrations ranging from 5×10^{-3} to 6.4×10^{-8} do not cause any increased contraction of the isolated intestinal segment over that produced by equivalent amounts of the sodium hydroxide solution used as the standard. At concentrations of 3.2×10^{-7} and 6.4×10^{-8} thyroxin in sodium hydroxide solution apparently tends to exert a repressant effect on the contraction produced by the hydroxide. These are the only concentrations tested at which any physiological effect at all was observed. It is evident from these results that thyroxin is not the constituent of the thyroid extracts which causes the contraction of the isolated intestinal segment described in the preceding paper.

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STUDIES IN CARBON MONOXIDE ASPHYXIA

I. The Behavior of the Heart

HOWARD W. HAGGARD

Investigations Performed for the United States Bureau of Mines, in the Laboratory of Applied Physiology, Yale University, New Haven[1]

Received for publication March 15, 1921

Acute oxygen deficiency produces a functional impairment of auriculoventricular conduction. This has been demonstrated by Sherrington, Lewis and Matthison and others (1), (2), (3), (4). The present investigation was undertaken to determine whether the same depression of conduction occurs in animals during carbon monoxide asphyxia; and further, whether this gas exerts a direct toxic action upon the heart, independent of the anoxemia.

It is highly probable that the toxicity of carbon monoxide is wholly dependent upon its union with hemoglobin, and thus upon asphyxia. But even so, the conditions under carbon monoxide differ significantly from those under inhalation of low concentration of oxygen. During carbon monoxide asphyxia the tension of oxygen in the arterial blood remains normal as long as pulmonary ventilation is maintained. It is the quantity which is decreased. On the other hand, during inhalation of low oxygen (as at a great altitude) both the quantity and tension of oxygen in the arterial blood are decreased.

This difference might lead to effects upon the heart varying from those observed in simple asphxyia by the investigators above mentioned.

General procedure. These observations were made upon dogs. A normal electrocardiogram[2] was obtained through leads to the right fore and left hind legs. With the electrodes still connected, the animal was placed in a glass chamber of 300 liters capacity (minus the mass of the animal in liters). An amount of carbon monoxide sufficient to produce the desired concentration was measured in; the accuracy of

[1] Published by permission of the Director of the United States Bureau of Mines.

[2] The apparatus used in this investigation was an Edelmann electrocardiographic outfit presented to the Medical School by Dr. Walter James of New York City.

the concentrations obtained by this method has been proven by previous work (5). With a dog of average size (8 to 10 kilos), the CO_2 in the chamber rose to 0.4 per cent in about 30 minutes and the oxygen fell an amount depending on the respiratory quotient. At the end of each 30 minutes the chamber was opened and rapidly cleared by an electric fan. It was then reclosed and a new charge of gas introduced. The temperature of the chamber rose only a few degrees above that prevailing in the room. Throughout the period of gassing, electrocardiographic tracings were taken at short intervals. In a few experiments respiratory tracings were obtained by means of a pneumograph. To determine the percentage combination of the hemoglobin with carbon monoxide the carmine method of Haldane was used (6). Blood was drawn from the ear.

Rapid fatal asphyxia. In the first seven experiments the asphyxia was carried to a fatal termination in a period of 25 to 40 minutes. The concentration of carbon monoxide ranged from 45 to 70 parts in 10,000 of air.

The general course of the animals' behavior was similar in all of the experiments. The usual excitement stage,—the whole course of events closely resembling ether anesthesia,—was followed by increasing unsteadiness on the feet, depression, and finally unconsciousness. Respiration became noticeably augmented soon after the gassing was started, and developed into dyspnoea which reached its height shortly before unconsciousness developed, and then passed into irregular, or even Cheyne-Stokes breathing. Following this, indications of respiratory failure soon developed. The gasps, which previously had been violent, became slower and feebler until finally respiration ceased entirely. The heart continued to beat for several minutes thereafter.

Until the approach of respiratory failure, the electrocardiographic findings were as follows: The heart rate increased almost from the first. Ventricular extra-systoles occurred in many cases. The T wave became greater in height, as in the observations made by Lewis and Matthison (2) during asphyxia of the spinal cat. In our experiments, however, there was almost uniformly a period of inversion of the T wave, which occurred near the height of the respiratory augmentation. (Note figures 1 and 2.) The heart rate decreased gradually as the volume of pulmonary ventilation lessened in the late stage of the asphyxia.

With the failing respiration the auricular wave, *P*, ceased to register during the expiratory pauses. A peculiar type of respiratory arrhyth-

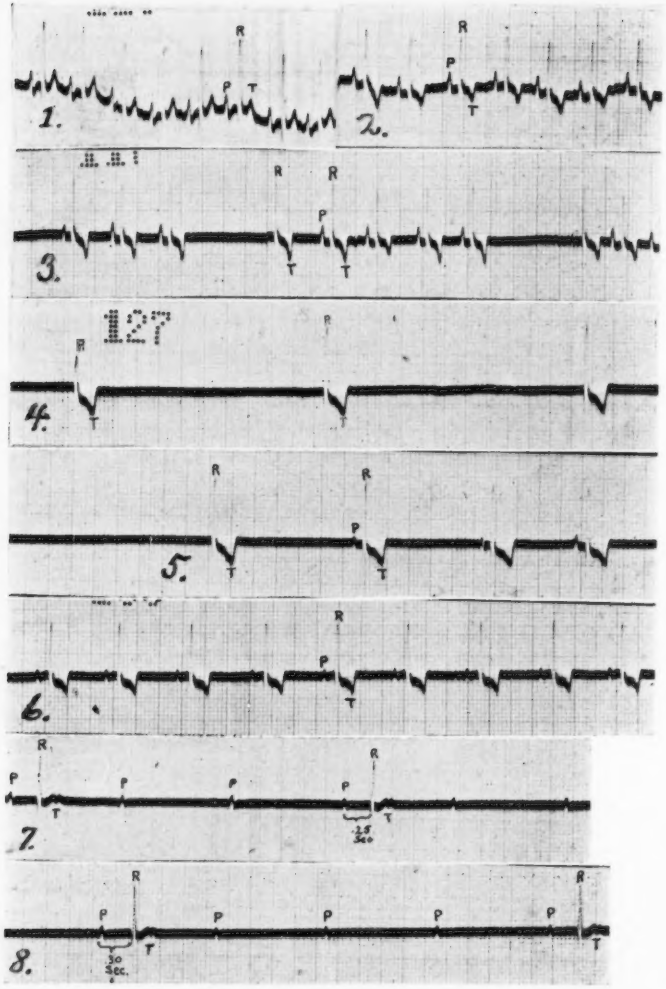


Fig. 1. From dog 1, after 10 minutes exposure to CO. Rate 172 per minute. P–R interval 0.11 second.

Fig. 2. From dog 1, after 18 minutes' exposure to CO. Rate 136. P–R interval 0.11 second. Showing inversion of T wave.

Fig. 3. From dog 1. Type of arrhythmia developed during respiratory embarrassment. No indication of delayed a–v conduction. Cessation of auricular beat during respiratory pause with escape of ventricle. This is seen more clearly in figure 10, which gives respiratory tracing.

Fig. 4. From dog 1. Cessation of auricular beat at time of respiratory failure. Ventricular rate 23 per minute.

Fig. 5. From dog 1. Record continuation of no 4, showing return of auricular wave and increase in cardiac rate.

Fig. 6. From dog 1. Record taken 90 seconds after no. 5. Cardiac rate 91 per minute. P–R interval 0.12 second.

Fig. 7. From dog 1. Development of 3–1 heart block. Auricular rate 59 per minute. P–R interval 0 25 second.

Fig. 8. From dog 1. 4–1 heart block. Auricular rate 59 per minute. P–R interval 0 30 second.

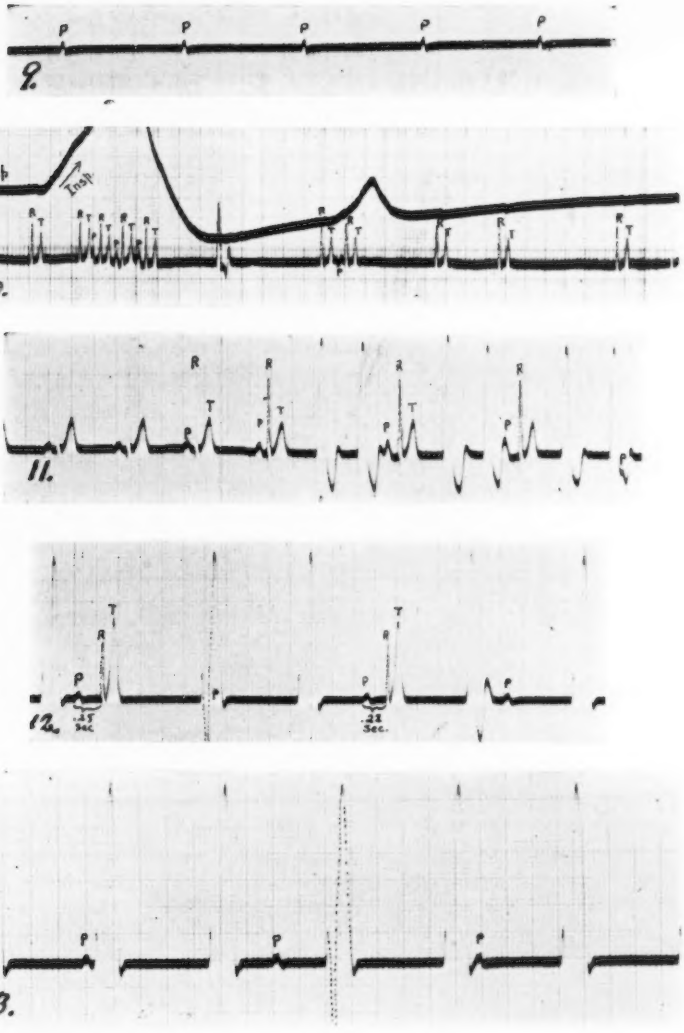


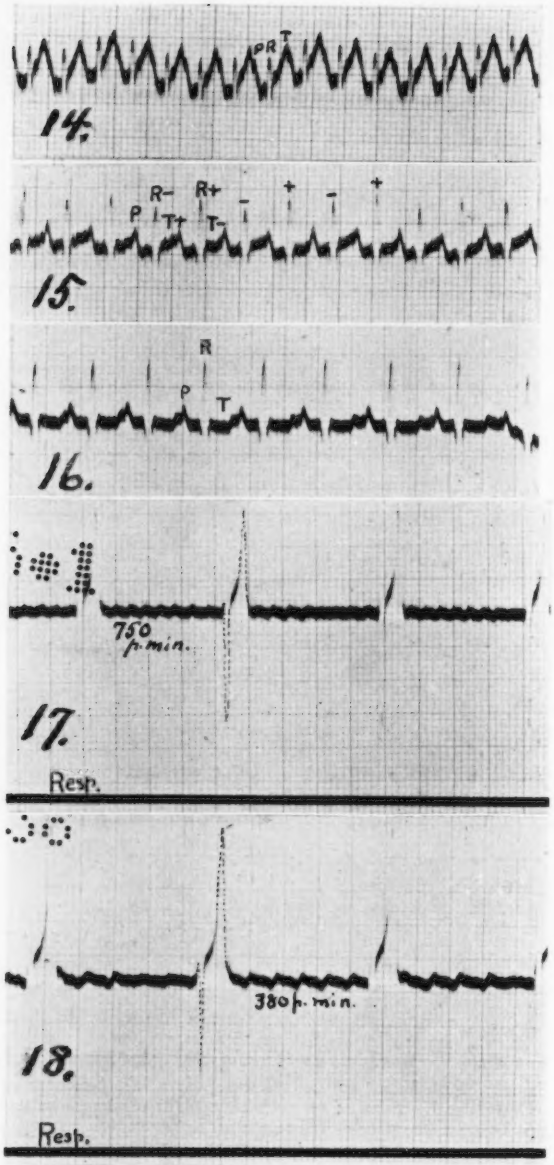
Fig. 9. From dog 1. Complete stoppage of ventricle 5½ minutes after respiratory failure. Auricular rate 59 per minute.

Fig. 10. From dog 6. Type of arrhythmia which develops during respiratory failure. Rapid rate with P wave present, during inspiration Slow ventricular rate, without P wave, during respiratory pause.

Fig. 11. From dog 4. Type of ventricular extra-systoles which develop at the height of the gassing.

Fig. 12. From dog 4; 2–1 heart block, with ventricular extrasystoles. Ventricular rate 48 per minute.

Fig. 13. From dog 4. Complete heart block Auricular rate 38 per minute. Ventricular rate 69 per minute. Origin of ventricular wave other than nodal.



Figs. 14, 15 and 16. Records from dog 9. CO preceded by atropine. Alternation of R and T waves in record 15. This is absent in 14 and 16, which were taken respectively 5 minutes before and after record 15.

Figs. 17 and 18. From dog 6. Taken during complete block. Auricular rate in 17 is 750 per minute; rhythmatic. In 8 the auricular rate is 380 per minute and the waves coarser.

mia developed. With inspiration the heart beat rapidly and the *P* wave was present with no evidence of delayed a-v conduction. During expiration and the following respiratory pause, the P wave was absent and the ventricular rate decreased. Ventricular complexes, apparently of nodal origin, appeared, and continued until the auricle became active with the next inspiration (figs. 3 and 10).

With the complete cessation of respiration the P wave disappeared from the tracings and the nodal ventricular beats assumed a rate of 23 to 40 per minute (fig. 4). By the end of the following minute, evidence of auricular activity had returned with little indication of delay in conduction (fig. 5). With the renewed activity of the auricle, the heart rate increased to 70 or 100 beats per minute (fig. 6). Within the next 2 minutes, delay of a-v conduction became evident in a lengthening of the P-R interval.

From this point two types of activity were presented by the different animals. In one type the impairment in a-v conduction became greater and partial heart block developed, passing through the stages of 1–3 and 1–4 (figs. 7 and 8) to complete block. The ventricular rate gradually became less, until at 4 or 5 minutes after respiratory failure all evidence of ventricular activity had ceased, and the P wave alone registered with a rate ranging from 40 to 60 per minute (fig. 9). This wave continued for 2 or 3 minutes after which the string of the electrocardiograph failed to give evidence of any cardiac activity.

In the second type the delayed conduction developed as in the first, and the various stages of heart block followed. But along with this condition, groups of regularly spaced ventricular extra-systoles occurred at intervals with increasing frequency throughout the records (figs. 11, 12 and 13). The ventricular complexes continued after the P wave had ceased to register. Their rate became slower and their contour more bizarre until they passed finally into a state of ventricular fibrillation.

Protocols 1 and 2 are typical of acute asphyxia.

In one of the seven animals during the period of complete block the auricle presented a rhythmic rate of approximately 750 per minute. The waves gradually slowed during 3 minutes, after which they became irregularly spaced and finally ceased (figs. 17 and 18). The ventricular complexes continued until ventricular fibrillation supervened.

In acute carbon monoxide asphyxia, fatal in periods of less than an hour, the anoxemia produced by the combination of hemoglobin with carbon monoxide is not sufficient in itself to impair a-v conduction. It is only after the great oxygen deprivation caused by failure of respiration that this development occurs.

Protocol 1. Experiment 1. Rapid carbon monoxide asphyxia. Dog 1. Male, 7 kilos. Gassed in 65 parts of carbon monoxide in 10,000 of air

TIME	REMARKS	ELECTROCARDIOGRAPHIC RECORD
min.		
0	Normal record taken. Gas started	Rate 108 per minute. P–R interval 0.12 second. Moderate respiratory arrhythmia.
5	Respiration slightly augmented	Rate 135 per minute. T wave increased in height. P–R interval 0.11 second. No respiratory arrhythmia.
10	Respiration markedly augmented	Rate 172 per minute. P–R interval 0.11 second. (Fig. 1.)
15	Respiration greatly augmented. Animal unable to stand	Rate 210 per minute. P–R interval 0.11 second. T wave decreased in height.
18	Respiration Cheyne-Stokes type	Rate 135 per minute. T wave inverted. P–R interval 0.11 second. (Fig. 2.)
20	Respiration slow, labored and gasping. Animal unconscious	Respiratory arrhythmia. Auricular inhibition during respiratory pause with escape of ventricle. (Fig. 3.)
21	Respiration stopped	Auricular inhibition. Ventricular wave nodal origin 25 per minute. (Fig. 4.)
22		Return of auricular wave. P–R interval 0.12 second. Cardiac rate increasing. (Fig. 5.)
23½		Rate 91 per minute. P–R interval 0.12 second. (Fig. 6.)
25		3:1 heart block. P–R interval 0.25 second. Auricular rate 59 per minute. (Fig. 7.)
26		4:1 heart block. P–R interval 0.30 second. Auricular rate 59 per second. (Fig. 8.)
26½		Ventricle stopped. Auricular rate 59 per minute. (Fig. 9.)
27½		No movement of string.
35	Heart's blood Hb. combined with CO, 86 per cent	

Respiratory failure, and its influence on the heart. The respiratory failure is apparently in the nature of a fatal apnoeavera. The hyperpnoea induced by the deficit of oxygen in the blood results in the elimination of an excessive amount of carbon dioxide. The respiratory quotient during this time is greater than one (as we know from other experiments). The excessive loss of CO_2 has a tendency finally to depress respiration. The respiratory stimulation therefore becomes increasingly dependent upon the deficit of oxygen. A point develops

Protocol 2. Experiment 4. Rapid carbon monoxide asphyxia. Dog 4. Male, 9 kilos. Gassed in 60 parts carbon monoxide in 10,000 of air

TIME	REMARKS	ELECTROCARDIOGRAPHIC RECORD
min.		
0	Normal record taken. Gas started	Rate 96 per minute. P–R interval 0.12 second.
5	Respiration slightly augmented	Rate 126 per minute. P–R interval 0.12 second.
10	Respiration greatly augmented	Rate 170 per minute. Numerous ventricular extrasystoles. P–R interval 0.12 second.
20	Respiration irregular, somewhat labored	Rate 152. P–R interval 0.12 second.
22	Respiration gasping	Rate 125 per minute. P–R interval 0.12 second Paroxysm of ventricular extra-systole. Decrease in auricular rate. (Fig. 11.)
23	Respiration stopped	No auricular wave. Series of irregular ventricular wave of origin other than nodal.
25		Auricular rate 68 per minute. Regular ventricular response. P–R interval 0.16 second. Numerous interpolated ventricular extra-systoles.
26		2:1 heart block. Auricular rate 50 per minute. P–R interval 0.22–0.25 second. Two or more extra-systoles between each normal ventricular response. (Fig. 12.)
28		Complete block. Auricular rate 38 per minute. Ventricular rate 69 per minute. (Fig. 13.)
29½		Auricular beat absent. Ventricular rate 54 per minute. Complex bizarre.
30		Ventricular complex 32 per minute.
32		Ventricular fibrillation.
40	Heart's blood Hb. combined with CO = 82 per cent	

when either the anoxemia ceases to increase sufficiently rapidly, owing to a flattening of the curve of carbon monoxide absorption, or the respiratory center becomes fatigued or less sensitive to the anoxemic stimulation. The CO_2 of the blood has become abnormally low, and the C_H is consequently decreased also. With the failure of the oxygen deficiency stimulus, respiration ceases, since the normal CO_2 stimulus is now absent.

With the decrease in pulmonary ventilation carbon dioxide reaccumulates to some extent in the blood. The blood alkali at this time has

fallen much below normal (evidence of this will be presented in a later paper) and for this reason, the C_H of the blood rises rapidly with the increase in CO_2. The respiration center fatigued or depressed through the excessive anoxemia to which it has been responding, fails to be stimulated by the rising C_H. As will be seen later it can be driven to further activity by a very considerable increase in the CO_2 of the blood induced through forced inhalation of this gas in proper dilution.

The fatigued cardio-inhibitory center, apparently, maintains its power of functioning after the respiration has failed. Its action is seen in the inhibition of the auricle at this time. This phenomenon, as noted later, is prevented by removing vagal action through injections of atropine prior to gassing. With the further advance of the anoxemia this center also loses its power of functioning and the auricle is freed from the inhibition. The various cardiac activities from this time on are purely those due to the action of oxygen deficiency upon the heart itself.

Influence of atropine upon the cardiac events. As has been suggested in the previous section, atropine abolishes the period of auricular cessation which occurs during the asphyxia at the time of respiratory failure. In four animals, atropine, $\frac{1}{60}$ gr., was administered hypodermically prior to the gassing which was carried out at a concentration of 50 parts in 10,000 of air.

The heart maintained a rapid rate until the time of respiratory failure. Following this, the rate slowed, the P-R time increased and a-v block developed, but without the stage of auricular cessation noted in the unatropinized animals. The dying heart ended in ventricular fibrillation.

In one of the animals, a short period of alternation involving both the R and T waves developed at the time of greatest respiratory augmentation. This is illustrated in figure 15. Figures 14 and 16 precede and follow this respectively by periods of 5 minutes. Neither gives indications of alternation.

The development of the deviation in the direction of the T wave, as noted previously, was unaffected by atropine.

Protocol 3 summarizes the findings from an experimental asphyxia preceded by atropine injection.

The heart after long exposure to carbon monoxide. The length of time during which the animal is subjected to deprivation of oxygen is a factor in bringing about pathological changes quite as important as the degree of anoxemia. For the investigation of this point, three

Protocol 3. Experiment 9. Carbon monoxide asphyxia after administration of atropine ($\frac{1}{50}$ gr.). Dog 9, female, 14 kilos. Gassed in 50 parts of carbon monoxide in 10,000 of air

TIME	REMARKS	ELECTROCARDIOGRAPHIC RECORD
min.		
0	Atropine given	
5	Record taken and gassing started	Rate 143 per minute. P–R interval 0.14 second.
10	Respiration rapid and somewhat jerky	Rate 193 per minute. P–R interval 0.14 second. T wave increased in height
15	Respiration greatly augmented	Rate 272 per minute. (Fig. 14.)
20	Respiration gasping	Rate 214 per minute. Alternation in height of T and R waves. P–R interval 0.14 second. (Fig. 15.)
25	Occasional gasping	Rate 167 per minute. P–R interval 0.14 second. No evidence of alternation. (Fig. 16.)
26	Respiration stopped	Rate 152 per minute. P–R interval 0.14 second.
27		Rate 152 per minute. P–R interval 0.16 second.
28		Rate 96 per minute. P–R interval 0.16 second.
29		Rate 76 per minute. P–R interval 0.20 second.
30		3:1 block auricular rate 62 per minute. P–R interval 0.30 second.
31		4:1 heart block auricular rate 48 per minute. P–R interval 0.28 second.
33		Auricle stopped. Ventricular complex bizarre; 42 per minute.
35		Ventricular complex very bizarre; 31 per minute.
36		Ventricular fibrillation.

dogs were gassed with 25 parts of carbon monoxide in 10,000 of air until death occurred. This covered periods of 5, 6½ and 7 hours. Electrocardiographic tracings were taken at intervals. No evidence of impairment of cardiac conduction developed until respiration had failed. The picture presented was essentially similar to that of animals under rapid asphyxia. The development of heart block, however, occurred and passed off somewhat more quickly. Ventricular fibrillation developed more quickly after respiratory failure than it did in those animals with shorter asphyxia. Protocol 4 is a typical experiment of this type.

In the gassings covering periods of several hours compensatory changes develop that tend somewhat to neutralize the time element.

Protocol 4. Experiment 14. Dog 14. Male, 6 kilos. Gassed in 25 parts of carbon monoxide in 10,000 of air

TIME	REMARKS	ELECTROCARDIOGRAPHIC RECORD
min.		
0	Normal record. Gas started	Rate 109. P–R interval 0.14 second.
60	Noticeable augmentation of respiration	Rate 164. P–R interval 0.14 second.
120	Extremely labored respiration	Rate 208. P–R interval 0.14 second. T wave increased in height.
180		Rate 220. P–R interval 0.12 second.
240	Cheyne-Stokes respiration	Rate 216. P–R interval 0.12 second. Slight respiratory arrhythmia. T wave diphasic.
300		Rate 196. P–R interval 0.14 second. Numerous ventricular extra-systoles. T wave inverted.
360		Rate 186. P–R interval 0.14 second. Ventricular extra-systoles.
390	Respiration gasping and irregular	Rate broken by ventricular extra-systoles.
410	Great respiratory embarrassment	Respiratory arrhythmia. Auricular inhibition during respiratory pause. P–R interval 0.16 second.
415	Respiration stopped	Rate 52 per minute. P–R interval 0.21 second.
416		Rate 52 per minute. P–R interval 0.31 second.
417		3:1 block. Bizarre ventricular waves. Auricle 46 per minute.
418		Complete block. Auricular rate 26 per minute. Ventricular rate 42 per minute.
419		Auricle stopped. Bizarre ventricular waves 28 per minute.
420		Ventricular waves 16 per minute.
421		Bizarre ventricular waves 46 per minute.
422		Bizarre ventricular waves. Irregular 74 per minute.
423		Ventricular fibrillation.
425		Ventricular fibrillation.

The heart during recovery. Three dogs were gassed rapidly as in the first series, electrocardiographic tracings being taken at intervals. When a condition of advanced respiratory embarrassment was reached the animals were removed from the gassing chamber. A short period of manual artificial respiration was necessary to prevent death and the animals were then allowed to recover. At intervals electrocardiographic tracings were taken.

The cardiac rate remained rapid during recovery and even after the animal was apparently completely normal again, 3 or 4 hours later. The T wave continued in the direction opposite to the normal after a lapse of 4 hours following gassing. In all three of the animals the T wave had assumed its normal position at the end of 24 hours and all evidence of tachycardia had passed.

Three other animals were permitted to pass into the stage of complete respiratory failure and remain so until partial heart block had developed. The attempt was then made to resuscitate the animals by means of a treatment recently devised in this laboratory (7). It consists in inhalation of 8 or 10 per cent CO_2 in oxygen, initially under artificial respiration, and then under spontaneous respiration stimulated by the CO_2. Recovery was successful with two of the animals. Electrocardiograms could not be taken during the vigorous breathing induced by the CO_2 in the inhalation. But after termination of the inhalation when the animal had quieted sufficiently, after 10 to 18 minutes, to allow an electrocardiographic record to be taken, all evidence of impairment of conduction had passed off. One animal exhibited a normal curve with only a moderate tachycardia and rather pronounced respiratory arrhythmia. The second animal which had passed to a somewhat greater stage of heart block (1–4) showed numerous ventricular extrasystoles still persisting 2 hours after the recovery. The animal's later condition was not followed, but there was no reason to doubt complete recovery.

Asphyxia when respiration is sustained by CO_2. The extent to which the impairment of conduction was due to cessation of respiration was investigated by preventing respiratory failure by means of inhalation of 7 per cent carbon dioxide. At the moment of removal from the gassing chamber the two animals used had respectively 82 and 84 per cent of the hemoglobin in combination with carbon monoxide. They were replaced in the chamber in an atmosphere containing carbon monoxide plus carbon dioxide. Respiration continued actively, and the absorption of carbon monoxide progressed to a higher degree than has ever otherwise been observed in this laboratory. One animal died after 14 minutes due to cardiac inhibition. Administration of atropine would undoubtedly have prevented this. The heart's blood showed 91 per cent of the hemoglobin combined with carbon monoxide. The second dog was removed after an exposure of 12 minutes with 93 per cent of its hemoglobin combined with carbon monoxide. This animal died 6 minutes after removal from the chamber apparently from respi-

ratory failure, presumably from inadequate CO_2. Unfortunately no tracing was obtained at this time. While in the CO_2 atmosphere neither animal showed any evidence of impairment of a-v conduction; for respiration was maintained under this stimulus.

The evidence from these experiments indicates clearly that the impairment of cardiac conduction under carbon monoxide is purely due to anoxemia. Carbon monoxide exerts no direct toxic action on the heart.

The experiments show another point of great interest, in that these two animals reached a percentage saturation with carbon monoxide much higher (6 to 15 per cent) than has ever occurred in this laboratory when carbon monoxide in air was used. Evidently the presence of carbon dioxide maintains respiration, prolongs life, and thus under the conditions above described increases the degree of carbon monoxide saturation.

Asphyxia wtih illuminating gas. It has been noted by Henderson and Haggard (7) that animals asphyxiated with illuminating gas (coal gas plus fattened water gas) diluted in air, die at a lower percentage saturation of hemoglobin with carbon monoxide than do animals exposed to a comparable concentration of pure carbon monoxide.

Electrocardiographic and pneumographic tracings were taken from animals gassed in illuminating gas diluted with air to a concentration of 50 parts of carbon monoxide in 10,000.

The course of events was essentially the same as that found under rapid asphyxiation with pure carbon monoxide of like concentration. There was, however, a much greater augmentation of respiration, and respiratory failure occurred at an earlier stage. The period of auricular cessation was slightly longer than in the animals exposed to pure carbon monoxide; the development of delayed conduction and a-v block was slower; and a greater time elapsed between the failure or respiration and the final cessation of cardiac activity or development of ventricular fibrillation.

Evidently the accessory toxic substances in illuminating gas exert a stimulating action upon respiration and thus hasten the development of acapnia, and respiratory fatigue and failure. But during short exposures there is no indication that these substances are directly and rapidly toxic. The delay in development of heart block may be accounted for by the greater oxygen supply (less carbon monoxide saturation) at the time of respiratory failure.

CONCLUSIONS

Death under carbon monoxide asphyxia is due to failure of respiration. This is in the nature of a fatal apnoeavera. The anoxemia resulting from the formation of carboxyhemoglobin induces excessive breathing; and respiratory failure follows the excessive loss of CO_2.

Oxygen deficiency caused by carbon monoxide, even in advanced asphyxia is not in itself sufficient to cause impairment of auriculoventricular conduction. Following respiratory failure, however, the increased anoxemia from this cause speedily results in the development of heart block through its various stages.

By restoring respiration and rapidly eliminating the carbon monoxide by means of inhalations of carbon dioxide and oxygen, cardiac conduction is restored to normal following the development of block.

The cardio-inhibitory center maintains its activity longer than does the respiratory center. This center is stimulated by the increased C_H which occurs during respiratory failure. From this there results a temporary cessation of auricular activity. This period of inhibition is prevented by the administration of atropine.

When respiratory failure is prevented by means of inhalations of 8 or 10 per cent carbon dioxide, the carbon monoxide combination with hemoglobin rises to an unusually high percentage without any evidence of impairment in a-v conduction. This indicates that there is no direct toxic action of carbon monoxide upon the cardiac conducting system.

Illuminating gas results in an earlier development of respiratory failure than does pure carbon monoxide in corresponding concentration.

Electrocardiographic records are given from two animals which differed from the rest in that one developed a transient period of alternation involving the R and T waves and the other presented, during the time of complete a-v block, a condition resembling auricular fibrillation or flutter.

In conclusion I wish to express my sincere thanks to Prof. Yandell Henderson for his advice and suggestions made during the course of this work.

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STUDIES IN NUTRITION

VIII. The Nutritive Value of the Proteins of Tomato Seed Press Cake

A. J. FINKS and CARL O. JOHNS

From the Protein Investigation Laboratory, Bureau of Chemistry, United States Department of Agriculture, Washington

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Large quantities of tomato[1] seeds and skins are at the present time discarded. These are by-products occurring in the manufacture of tomato catsup, soups and pastes. Rabak (1) has estimated that 1500 tons of dried tomato seeds could be obtained annually in this country. Tomato seeds contain approximately 22 per cent of a valuable oil suitable for table use (2), (3), (4). The press cake which remains after expelling the oil contains about 37 per cent of protein (N × 6.25). This has been used to some extent as a fertilizer and also as a cattle feed.

The isolation and chemical analysis of the proteins from the tomato seed are in progress in this laboratory. Preliminary experiments indicate the presence of two globulins differing chiefly in their nitrogen and sulphur content (5).

The nutrition experiments described in this paper with tomato seed press cake[2] show that its proteins are efficient for the normal growth of albino rats, and that the press cake is as valuable a protein concentrate as peanut, soy bean or cocoanut press cake.

Tomato seed press cake may also contain some fat-soluble vitamine, since normal growth was obtained on a diet in which the butter fat, which is usually incorporated to provide this vitamine, was replaced by an equivalent amount of lard. There is still some question, how-

[1] *Solanum esculentum.*

[2] The tomato seed press cake was furnished by J. H. Shrader, formerly with the Bureau of Plant Industry, U. S. Department of Agriculture. The seeds, previous to expelling the oil, were dried in direct heat rotary dryer at a temperature which did not exceed 60°C. The resulting press cake was ground to a meal which was incorporated in the rations used in our experiments.

ever, whether or not lard may be a source of fat-soluble vitamine. Daniels and Loughlin (6) have reported successful experiments in which lard was the only apparent source of fat-soluble vitamine in an otherwise complete diet. In a recent publication by Osborne and Mendel (7) it was shown that 28 per cent of lard, carefully rendered at a low temperature did not contain enough fat-soluble vitamine for normal growth. To explain these divergent results, Osborne and Mendel (7) offered the following tentative hypothesis:

"Must we assume for the present either that the lard from different sources varies in its content of fat-soluble vitamine, or that ether alone fails to extract it from the non-fat foodstuffs?"

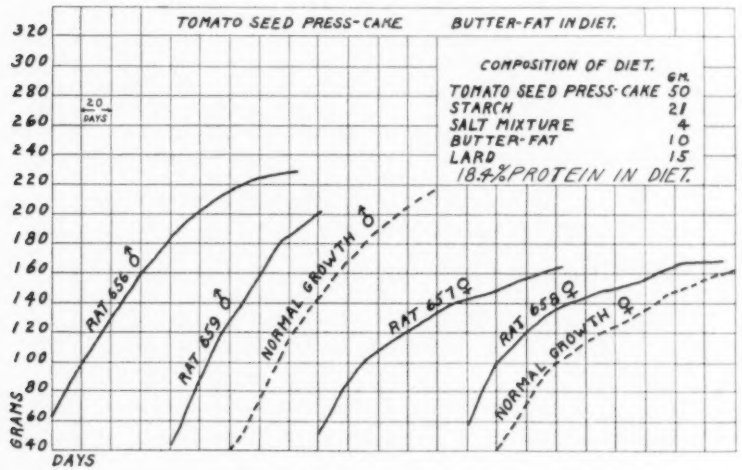

Chart 1

Drummond and his co-workers (8) have shown that the diet of the pig, part of the body from which the pig fat is taken, as well as the process of lard manufacture, all influence the fat-soluble vitamine content of the finished product.

It is also interesting to note that many of the nutrition experiments in which the proteins were biologically adequate, viz., soy bean (9), (10), peanut (11), (12), cotton seed (13), (14), (15), (16), and cocoanut (17), as in the case with the tomato seed, were also oil bearing seeds.

Experimental. A diet consisting of 50 parts of tomato seed press cake, 21 parts of commercial cornstarch, 15 parts of lard, 10 parts of

butter fat and 4 parts of the Osborne and Mendel salt mixture, when fed to albino rats, resulted in the normal rate of growth. These experiments indicate that tomato seed press cake contains a sufficient quantity of water-soluble vitamine for normal growth. Such a diet contained 18.4 per cent of protein. The results of these experiments are recorded on chart 1.

A similar diet, with the exception that the 10 parts of butter fat were replaced by an equivalent amount of lard, was also adequate for nor-

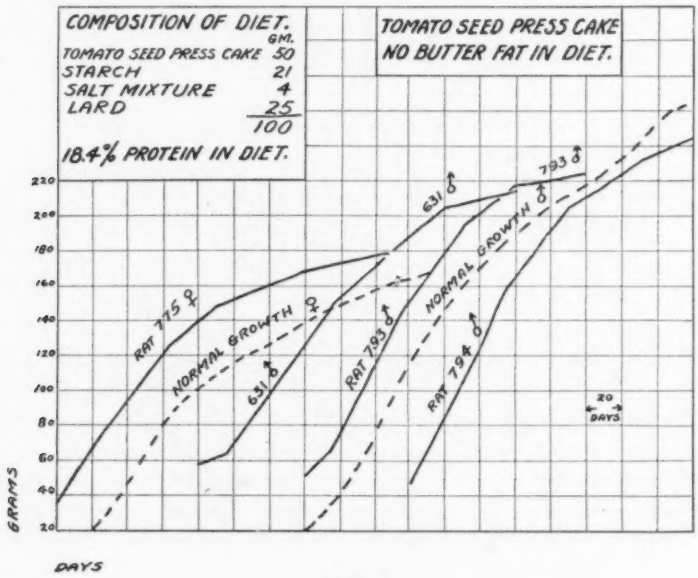

Chart 2

mal growth. The question of whether or not the residual oil in the tomato seed press cake or the press cake itself contained enough fat-soluble vitamine must be left in abeyance until it is definitely shown that the other dietary constituents are not sources of fat-soluble vitamine. In this connection it is interesting to note that Osborne and Mendel (18) found that 0.1 gram of dried tomato, furnished daily, contained enough fat-soluble vitamine for normal growth. The ether extract of dried tomato, however, was not potent and failed to promote renewal of growth in rats that had declined on a diet which was deficient in fat-soluble vitamine.

The results of our experiments are shown on chart 2.

SUMMARY

A diet in which tomato seed press cake furnished the sole source of protein and water-soluble vitamine enabled albino rats to grow at the normal rate. Such a diet was made adequate by the addition of starch, a suitable inorganic salt mixture, butter-fat and lard. Normal growth was also obtained when the butter fat of the above diet was replaced by lard.

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THE MODE OF ACTION OF LOW TEMPERATURES AND OF COLD BATHS IN INCREASING THE OXIDATIVE PROCESSES

W. E. BURGE AND J. M. LEICHSENRING

From the Physiological Laboratory, University of Illinois

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As a result of the work of Lavoisier (1) and of a great number of investigators (2) since his time, it is now known that a fall in the external temperature as well as cold baths increase oxidation in warm-blooded animals and decrease it in cold-blooded animals. The action of cold on the skin of warm-blooded animals produces reflexly an increased innervation of the muscles resulting in movements (shivering) or in the increase in tone. Several observers (3) have shown that unless the lowering of the temperature or the coldness of the bath is sufficient to cause shivering or muscular tension, no increase in oxidation results. Cold-blooded animals, on the other hand, have no heat regulating mechanism such as is found in warm-blooded animals and hence their heat production rises and falls with a rise and fall in external temperature.

The increase in heat production brought about by cold in warm-blooded animals is usually attributed to the additional heat produced by the action of the muscles. Voit believed that the increase in metabolism brought about by cold was due to a reflex stimulation of the muscles resulting in an increase in the inherent power of the muscle cells to metabolize.

We (4) had already found that whatever increased oxidation in the body, the ingestion of food, for example, brought about an increase in catalase, an enzyme possessing the property of liberating oxygen from hydrogen peroxide, by stimulating the alimentary glands, particularly the liver, to an increased output of this enzyme, and that whatever decreased oxidation, narcotics, for example, produced a decrease in catalase by decreasing its output from the liver and by direct destruction. Hence we naturally turned to catalase for an explanation of the increase in oxidation brought about by exposure of warm-blooded

animals to cold and for the decrease in oxidation on exposure of cold-blooded animals to low temperatures.

The warm-blooded animals used were dogs and the cold-blooded, turtles. The effect on the blood catalase of keeping these animals in a cold chamber as well as in hot and cold baths, and in baths at different temperatures was tried out.

The cold chamber was constructed large enough to accommodate a dog comfortably. A stream of fresh air was forced through the chamber continuously. Further provision was made for the animal to get fresh air by cutting a small window in the wall of the cold chamber through which the animal could poke its snout. The temperature of this chamber could be kept fairly constant over a period of several hours. Catalase determinations were made of the blood of the jugular before as well as at intervals after the dogs were placed in the chamber. The determinations were made by adding 1 cc. of the jugular blood to 50 cc. of neutral hydrogen peroxide in a bottle and the amount of oxygen liberated in 10 minutes was taken as a measure of the catalase content of the blood. The normal catalase content of the blood was established by making determinations on two or three successive days previous to performing the experiment.

The following experiment will illustrate the method as well as show the effect of cold on the blood catalase in vivo. A short-haired, adult dog weighing about 3 kilos was placed in the chamber at 2°C. and permitted to remain there for 3 hours. One cubic centimeter of the jugular blood of this dog prior to being placed in the chamber liberated 74 cc. of oxygen from 50 cc. of neutral hydrogen peroxide in 10 minutes. After he had been in the cold chamber for 3 hours, a similar amount of jugular blood liberated 100 cc. of oxygen from hydrogen peroxide in 10 minutes. The dog was then kept in a room at 22°C. for 17 hours and at the end of this time the catalase of the blood had returned to normal, that is, 1 cc. of the blood liberated 70 cc. of oxygen from hydrogen peroxide. This experiment was repeated using the same dog with comparable results.

The catalase content of the jugular blood of another short-haired dog, older and much fleshier than the preceding, was determined and 1 cc. of his blood was found to liberate 250 cc. of oxygen. After being in the chamber for 1½ hours, his blood liberated 278 cc. of oxygen and after 3 hours 293 cc. On keeping the dog for about 17 hours in a room at a temperature of 22°C. the blood catalase returned to normal.

E. Voit (5) showed that the metabolism of the pigeon may be doubled by removing its feathers. Rubner (6) found that the metabolism of a dog was greatly increased by the clipping of his hair. The following experiment was carried out using a very long-haired poodle dog to determine if cold would produce a greater increase in the blood catalase after his hair was clipped than it did before. One cubic centimeter of the jugular blood of the long-haired poodle dog was found to liberate 226 cc. of oxygen from neutral hydrogen peroxide in 10 minutes. The dog was kept in the cold chamber for 3 hours at 2°C. and at the end of this time it was found that the blood catalase had been increased by about 7 per cent. After the blood catalase of the dog had returned to normal, his hair was clipped and he was again placed in the chamber at 2°C. for 3 hours. It was then found that the cold increased the catalase of the jugular blood by about 16 per cent. By comparing these results, it may be seen that the percentage increase produced after the clipping was more than twice as great as it was before the clipping.

The following experiment was carried out to determine the effect on the blood catalase of exposing the same dog at different temperatures for the same length of time. Three catalase determinations were made using the jugular blood, one before the dog was placed in the cold chamber, another after he had been in the chamber for 3 hours at 2°C. and a third, 17 hours later during which time the dog was kept in a room at 22°C. Similarly catalase determinations were made after the dog had been kept in the cold chamber at 7°C., 15°C. and 22°C. respectively. The results of the determinations are shown in figure 1. The figures along the ordinate indicate percentage increase in catalase and those along the abscissa, time in hours.

It may be seen that the exposure of the dog for 3 hours in the cold chamber at 2°C. increased the catalase of the blood 35 and 36 per cent respectively in two experiments; that exposure at 7°C. increased it 18 per cent; exposure at 15°C. increased it 15 per cent and at room temperature (22°C.) practically no change in the catalase content of the blood was produced. It may be seen further that 17 hours after each experiment during which time the animal was kept in a room at 22°C., the blood catalase had returned to practically normal in all cases.

Rubner (7) and others have shown that cold baths greatly increase the oxidative processes; that this effect decreases with a rise in the temperature of the bath, disappearing entirely at 35°C. and again is increased at 44°C. The increase in heat production brought about

by cold baths is usually attributed to the additional heat produced in shivering, and that by the very hot baths to the warming of the cells.

The following experiments were carried out to determine the effect of very cold baths (3°C.) and baths at different temperatures on the blood catalase. The animals used were dogs. Approximately 200 liters of water were used for the bath. The dog, with the exception of his head and neck, was immersed in the water. There was very little struggling on the part of the animal. Upon removing from the bath, the animals were rubbed dry with a cloth and placed in a warm chamber at 30°C. In a short time the dog was warm and comfortable.

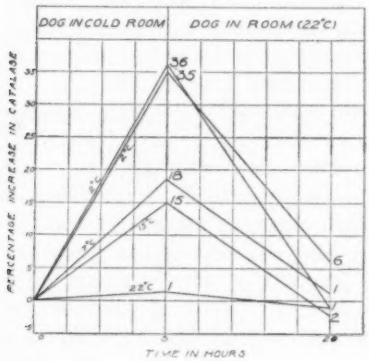

Fig. 1

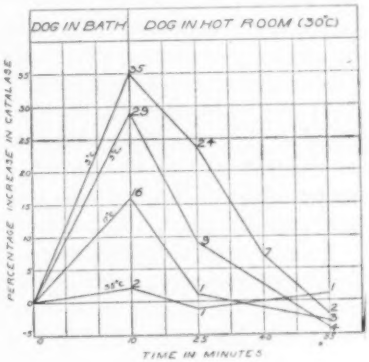

Fig. 2

Fig. 1. Curves showing the effect on the blood catalase of exposing the same dog to different degrees of cold.

Fig. 2. Curves showing the effect of baths at different temperatures on the blood catalase of the same dog.

Catalase determinations were made using the jugular blood of a medium-sized, short-haired dog. It was found that 1 cc. of the blood liberated 198 cc. of oxygen in 10 minutes from 50 cc. of neutral hydrogen peroxide. The dog was placed in the cold bath (3°C.) for 10 minutes. At the end of this time 1 cc. of the blood liberated 268 cc. of oxygen from hydrogen peroxide. The dog was rubbed dry and placed in the warm chamber. Fifteen minutes later 1 cc. of the blood liberated 246 cc. of oxygen; 30 minutes later, 212 cc. and 45 minutes later, 1 cc. of the blood liberated practically the same amount of oxygen as it did before the dog was placed in the cold bath, that is, the blood catalase had returned to its normal amount. Similar experiments were carried out using several different dogs with similar results.

The following experiment was carried out to determine the effect of baths at different temperatures on the blood catalase, using the same dog. The results are shown in figure 2. It may be seen that a bath at 3°C. for 10 minutes increased the blood catalase 35 and 29 per cent respectively in two experiments, the same dog being used; that a bath at 17°C. for 10 minutes increased the blood catalase 16 per cent; and a bath at 35°C. produced practically no change in the catalase content of the blood. It may be seen further that the blood catalase had returned practically to normal 45 minutes after the baths.

It is known that oxidation is increased in cold-blooded animals when the external temperature is raised and is decreased when the external temperature is lowered. The following experiments were carried out to determine the effect on the blood catalase of cold-blooded animals of raising and lowering the external temperature.

The cold-blooded animals used were turtles (Pseudemys concinna). Catalase determinations were made according to the method described in the first part of this paper. The blood used was taken from the aortic arches through a hole 2 cm. in diameter made in the plastron just over the heart. This hole was kept closed by means of a cork.

Several determinations were made using the same turtle which had been kept at ordinary room temperature (22°C.) and it was found that 1 cc. of blood liberated 790 cc. of oxygen in 10 minutes from 200 cc. of neutral hydrogen peroxide. This turtle was packed in crushed ice for 15 hours and at the end of this time 1 cc. of the blood liberated 270 cc. of oxygen from neutral hydrogen peroxide. One cubic centimeter of blood from another turtle was found to liberate 760 cc. of oxygen from neutral hydrogen peroxide in 10 minutes. This turtle was placed in warm water at 40°C. for 30 minutes. Upon removal from the warm water 1 cc. of the blood liberated 850 cc. of oxygen. Experiments similar to the preceding were carried out with comparable results.

The following experiment was carried out using the same turtle to determine the effect on the blood catalase of exposing the animal to cold as well as to heat. The animal was kept in a warm bath at 40°C. and later packed in crushed ice for 15 hours.

It may be seen in figure 3 that 1 cc. of the blood of the turtle while being kept at ordinary room temperature (22°C.) liberated 760 and 765 cc. of oxygen respectively from 200 cc. of neutral hydrogen peroxide in 10 minutes and that after keeping this turtle in a hot bath (40°C.) for 30 minutes the amount of oxygen liberated by the blood increased to 850 cc. It may be seen further that on keeping the turtle for the

following 6 hours at room temperature, the blood catalase returned to normal, that is, 1 cc. of blood liberated 765 cc. of oxygen from hydrogen peroxide in 10 minutes. On keeping the turtle packed in crushed ice for 15 hours, the blood catalase was greatly decreased, 1 cc. of blood

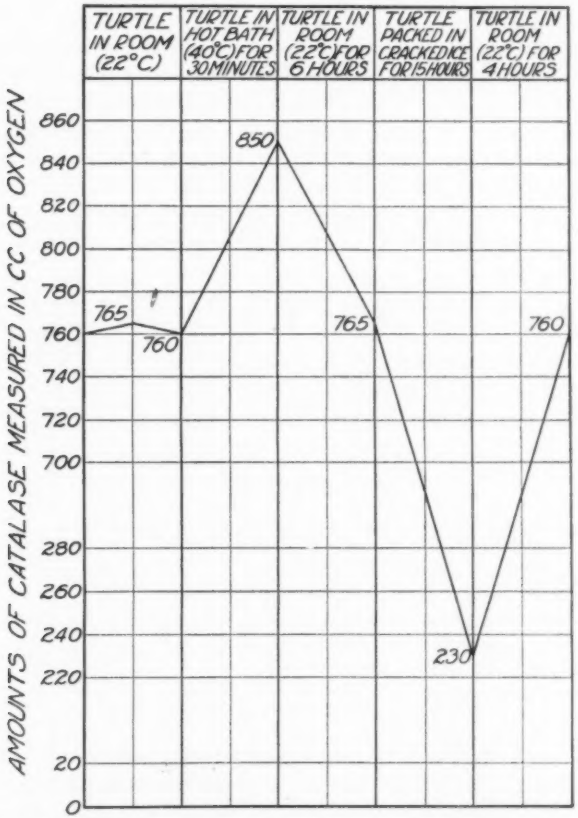

Fig. 3. Curves showing the effect of high and of low temperatures on the blood catalase of the same turtle.

liberating only 230 cc. of oxygen, and that 4 hours later, during which time the animal was kept at room temperature, the blood catalase had returned to normal. It should be said in this connection that the turtle had also become normal so far as its activity was concerned.

SUMMARY

Low temperatures and cold baths produce an increase in the blood catalase of warm-blooded animals and a decrease in cold-blooded animals, in keeping with the fact that cold increases oxidation in warm-blooded animals and decreases it in cold-blooded animals. An increase in the external temperature increases the blood catalase in cold-blooded animals in keeping with the fact that it increases the oxidative processes.

The stimulating effect of low temperatures on catalase production in warm-blooded animals decreases with a rise in temperature, disappearing at room temperature (22°C.) in keeping with the fact that the stimulating effect of cold on metabolism decreases with a rise in temperature. Baths at 35°C. produce no increase in oxidation in warm-blooded animals and it is shown in this paper that such baths do not increase catalase.

The increase in oxidation in warm-blooded animals on exposure to cold is attributed to an increase in catalase, and the decrease in oxidation in cold-blooded animals on exposure to cold, to a decrease in catalase. The increase in oxidation in cold-blooded animals occurring with a rise in external temperature is attributed to an increase in catalase.

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STUDIES ON THE CONSECUTIVE PHASES OF THE CARDIAC CYCLE

I. The Duration of the Consecutive Phases of the Cardiac Cycle and the Criteria for their Precise Determination

CARL J. WIGGERS

From the Department of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio

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During the course of investigations pertaining to the behavior of the heart under certain experimental pathological conditions, it became evident that the compensatory phenomena of the ventricles involve not only changes in the *vigor* of the ventricular contractions but alterations also in the *duration* of certain phases of its contraction and relaxation processes. In order to determine how far these mechanisms are normally operative in adapting the work of the heart to differing normal conditions and how far they are held in reserve until abnormal conditions arise, it became necessary to establish how the duration of each consecutive phase of the cardiac cycle can be altered in length under normal conditions. This not only involves a subdivision of the periods of systole and diastole into still shorter phases but also necessitates the establishment of precise criteria for the accurate calculation of the length of these consecutive phases.

METHODS

An analysis of the consecutive phases of the cardiac cycle can be most successfully accomplished by a study of pressure curves optically recorded from the cardiac chambers and vascular system. During the course of my work, extending over a period covering the last five years, a total of about 6 kilometers of tracings showing simultaneous pressure curves from two portions of the vascular system have accumulated. These records include curves obtained under normal as well as various experimental conditions produced in 192 different dogs. In addition to this unusually large amount of material, a further series

of 18 experiments was recently added in which three simultaneous pressure curves from the auricle, ventricle and aorta were simultaneously recorded. In these experiments, in which the heart within the pericardium was exposed, three optical manometers of essentially the same type as described by the writer (1) in 1914, were inserted as follows: One into the left ventricular cavity through the muscular wall, a second into the left auricle through the tip of the auricular appendage and a third, via the innominate artery, into the aorta so that its tip lay near the aortic valve. Each manometer was rigidly fixed by clamps so that no movements of the light beams occurred when the cannulae stopcocks were closed.

In endeavoring to establish precise time relations by the use of several curves simultaneously recorded by such optical projections, certain difficulties arise. In the first place, attention must be paid to the shifting of recorded points due to parallax. Methods of obviating such errors have been discussed by C. Tigerstedt (2), Garten (3), and lately again by Straub (4). For various reasons, the methods suggested for obviating such displacement or for correcting it could not be employed in this work. The following arrangement was used: Each manometer was illuminated by a separate arc light, the only source of illumination still available which is capable of producing satisfactory curves on bromide paper moving more than 100 mm. per second. For anatomical reasons only one manometer (usually the ventricular) could be so arranged that the reflection center of the mirror was directly in line with the camera lens. The other manometers, i.e., the auricular and aortic, were faced away from the photokymograph and the incident beams projected on their mirrors were reflected to two other "first surface" mirrors which were vertically superimposed and so arranged that the light centers were in direct line with the vertical camera slot. When care was taken in the alignment, subsequent photographic checks on stationery paper showed no displacement of synchronous points due to parallax. Needless to say, such checks were always made and appropriate corrections carried out when needed.

A second difficulty arises in the evaluation of the time differences due to a delay of pressure transmission within the vascular system. In the case of comparisons between arterial and ventricular curves, for example, such correction has usually been made by measuring the distance of the arterial cannula from the aortic orifice and calculating the delay on the basis that the pressure wave travels with a velocity of

approximately 7 meters per second. Such corrections can not be considered very exact. In the first place, the velocity of the pressure transmission changes during the cardiac cycle, being modified, at least, by the momentary changes in the volume elasticity coefficient. This is illustrated in figure 3, in which the delay in transmission of several points of the pressure curves is shown. The upper curve was taken from the innominate artery, 6 cm. from the semilunar valves; the lower curves represent pressure changes quite close to the valves. If we estimate the delay at obviously similar points such as D and H, it will be found that the delay at point D equals 0.0187 second, whereas at point H it is equivalent to 0.0034 second. Estimating the velocity on the basis of post-mortem measurements above noted, it is found that the velocity of pressure propagation is 3.2 meters per second at the point D, and 17.6 meters per second at point H.

Furthermore, there is great difficulty in measuring with exactness the distance between the aortic orifice and the arterial cannula, partly because it is difficult to be quite certain as to the precise plane that functionally separates aorta and ventricle; partly also because the length of the aorta apparently changes with the fullness of the vessel and the changing position of the heart during experimental work. It is my impression that post-mortem measurements can not be made with sufficient exactness for use in time corrections involving a few σ.

It is therefore not surprising that various careful investigators, such as Piper (5), C. Tigerstedt (2) and Garten (6), each believing his technic unimpeachable, should have arrived at somewhat different interpretations as to synchronous events in the several pressure curves. Since it is probably as yet not possible always to rely implicitly on time corrections made in this way, all interpretations must be tempered by a consideration as to whether the dynamic events thus indicated are possible. While synchronous events on different curves can be established without difficulty in such records as are used to illustrate this paper, it must be frankly acknowledged that I have many tracings in my possession in which adherence to strict corrective processes, such as outlined above, would force one to admit that a condition of dynamic chaos must exist in the cardiovascular mechanisms, and one could point out many dynamic absurdities in published records of other investigators were one inclined to be critical.

SUGGESTED SUBDIVISIONS OF THE CARDIAC CYCLE

The term *systole* is generally used to designate the period of muscular contraction and the term *diastole*, the combined period of physiological relaxation and any possible additional phase of quiescence. This division of the cardiac cycle has proven so useful in studying the cardiac cycle that it seems desirable to adhere to it. A further subdivision of these two *periods* has, however, been suggested, on separate occasions, by different investigators. To promote clarity these will be referred to as *phases* of systole and diastole in this article.

Subdivision of systole. The earlier work of Chauveau and Marey, Hürthle and V. Frey suggested the subdivision of ventricular systole into two phases: an Anspannungszeit and Austreibungszeit. The latter phase has been usually referred to as the ejection phase by English writers but it has been more difficult to find a concise and accurate term by which to designate the Anspannungszeit. The phrase "period of rising tension" is too long and the term "presphygmic period" is unfortunately inaccurate since, as Frank (7) first showed, there is a well-marked sphygmic oscillation during this phase. Frank (8) has also pointed out that the dynamic reactions of the ventricle closely correspond to those of an after-loaded skeletal muscle which contracts first isometrically and later isotonically. On this basis I suggested the term isometric phase in place of the period of rising tension. Frank has also definitely pointed out, however, that during the ejection phase, the ventricle, unlike an after-loaded skeletal muscle, is not contracting under an absolutely constant tension and that it therefore contracts only in an approximately isotonic fashion. Starling (9) proposed the term auxo-tonic (that is, acting under an increasing tension) as expressing the nature of ventricular contraction during the ejection phase. This phrase, however, is also not quite descriptive of the dynamic conditions of the normal heart which contracts first against an increasing but later against a decreasing load. If a general term is desirable, the phrase "allasotonic" (i.e., acting under a variable tension) would seem more appropriate. On the whole, however, it will be just as well perhaps to refer to the two phases of ventricular systole as the isometric and ejection phases. In the light of other investigations, it is necessary to consider the advisability of further subdivision. Thus, Piper's interpretation of the optical ventricular pressure curve (5), supported also by the work of Dean (10) and my own analysis of the pressure curves, indicates that the a-v valves are

not closed effectively until a slight elevation of intraventricular pressure has taken place. If this is the case, then the period rising tension may include a pre-isometric as well as an isometric phase. So also it is possibly necessary to divide the ejection phase into an early phase of maximum ejection and a later phase of reduced or absent ejection. Frank (8) has directed attention to the fact that the aortic pressure rises during the early portion of ejection and falls during the latter portion of this phase because the peripheral outflow from the arterial system exceeds the ventricular volume ejected into the aorta during this latter phase. This can only mean that the ventricle must eject a smaller quantity of blood toward the end of systole. Such a reduced ejection is manifest also in normal volume curves reported by Henderson (11), de Heer (12) and Straub (13), and according to Patterson, Piper and Starling (9) such curves may show "some justification for the old idea that the latter portion of ventricular systole represents a 'Verharrungszeit' or 'Rückständage Contraction,'" i.e., a condition in which the ventricles remain contracted without expelling any blood.

Phases of diastole. On the basis of pressure curves Hürthle (14) subdivided diastole into a phase of rapidly declining tension and a diastolic inflow phase. de Heer (12) points out that the former represents a phase in which the ventricle relaxes with all valves closed, i.e., isometrically. Accordingly, the interval between the closure of the semilunar valves and the opening of the a-v valves might be designated as the isometric-relaxation phase. According to the volumetric studies of Henderson and his co-workers (11), the inflow, starting at the opening of the a-v valves, does not continue with equal rapidity until the end of diastole, provided the period of diastole is sufficiently long; on the contrary, there appears a phase of relative stasis or diminution in the rate of blood flow from auricle to ventricle. This interval they have designated as diastasis and originally added as a third major period of the cardiac cycle. For reasons already indicated, it seems preferable to consider this as a third phase of diastole.

More recent analyses of the pressure and volume curves of the ventricles indicate that the phase of declining tension mentioned by Hürthle must be further subdivided. Finally, the experiments of Straub (13), Patterson, Piper and Starling (9), and also those of Gesell (15) indicate that auricular contraction affects the dynamics of ventricular efficiency sufficiently to warrant its inclusion as a last phase of ventricular diastole. As these suggested divisions of the cardiac cycle are not as yet universally accepted, we are not only confronted with the task of

determining the demarcation of the several consecutive phases of the ventricular cycle but are compelled also to inquire into the necessity, as well as the desirability, of these suggested subdivisions.

THE CONSECUTIVE PHASES OF THE VENTRICULAR CYCLE, AS INDICATED BY THE PRESSURE CURVES

The consecutive changes in pressure occurring within the left auricle, left ventricle and root of aorta of a vigorously beating heart are shown in figures 1 and 2. The technical data are given in the legends. As a basis for initiating analysis, five lines are drawn to indicate the customary subdivisions that have been used by others and myself in analyzing the cardiac cycle. Lines *1–2* demarcate the interval usually designated as the isometric contraction phase; *2–3* limit the ejection phase; 3–4 comprise the early diastolic relaxation phase; *4–5* include the rapid inflow phase and the balance of the cycle comprises the phase of diastasis terminating in auricular systole. In considering the time limits of these phases, the desirability of further subdivision will be discussed.

The demarcation of the isometric phase. If, as in figures 1 and 2, we consider the isometric phase of contraction as beginning with the onset of the pressure rise, we are at once confronted with the questions as to whether the a-v valves are closed prior to ventricular systole and, if not, whether the isometric contraction may be regarded as beginning at this point.

The idea that the a-v valves are closed, not by the elevation of intraventricular pressure following ventricular systole but by the cessation of a jet of blood forced into the ventricle during auricular systole, appears to have been first suggested by the observations of Baumgarten (16) in 1843. This investigator showed that when a stream of water directed against the valves is suddenly stopped, they immediately float into a position of closure so that the heart may be inverted without leakage of fluid through them. These observations have been confirmed by Henderson and Johnson (17) in the case of valves mounted as naturally as possible in a glass beaker. While these experiments leave no doubt that the auricular and ventricular valves *can* float into apposition by the sudden interruption of a vigorous stream, it does not necessarily follow that a similar mode of closure occurs in the beating heart in which the force of auricular systole must be very much less and the dynamic conditions are somewhat different. Direct records of the movements of the valvular cusps in a beating heart recorded by Dean

(10) indicated that while the force of auricular systole is indeed capable of floating the valves toward a position of closure, a complete approximation accompanied by sound vibrations apparently does not take place unless a subsequent ventricular systole follows.

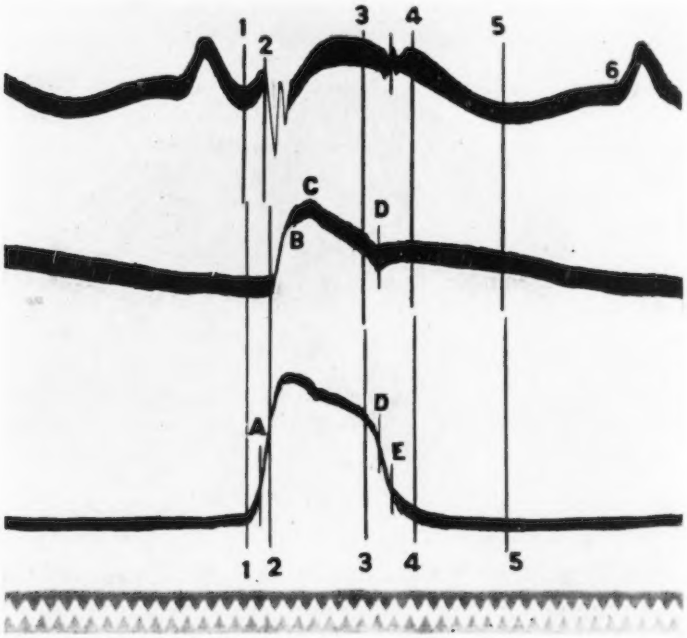

Fig. 1. Synchronous records of intra-auricular pressure (upper); pulmonary arterial (middle); right ventricular pressure (lower). Tuning fork 0.02 second; *1–2*, isometric contraction phase; *2–3*, phases of maximum and reduced ejection; *3–D*, proto-diastolic phase; *D–4*, isometric relaxation phase; *4–5*, rapid inflow phase; *5–6*, diastasis. Further description in text.

The chief argument advanced by those who incline to the theory of pre-systolic closure seems to be that, in such cases, a slight regurgitation of blood into the auricle must inevitably result unless the valves are closed before ventricular systole begins. The writer has not been able to follow clearly the logic involved. Henderson and Johnson, for example, liken the regurgitation to the volume of air displaced from a room into a corridor when a door closes by a hinge movement. Whether

such a displacement should be considered as a regurgitation in the sense that the term has come to assume, depends, of course, on whether the door frame or the door itself is considered as the line of division between the room and the corridor. In any case, no considerable volume could be displaced auricle-ward, but such a displacement as occurs must cause some elevation of auricular pressure. Are there any indications on the pressure curve that this takes place? Even a casual inspection

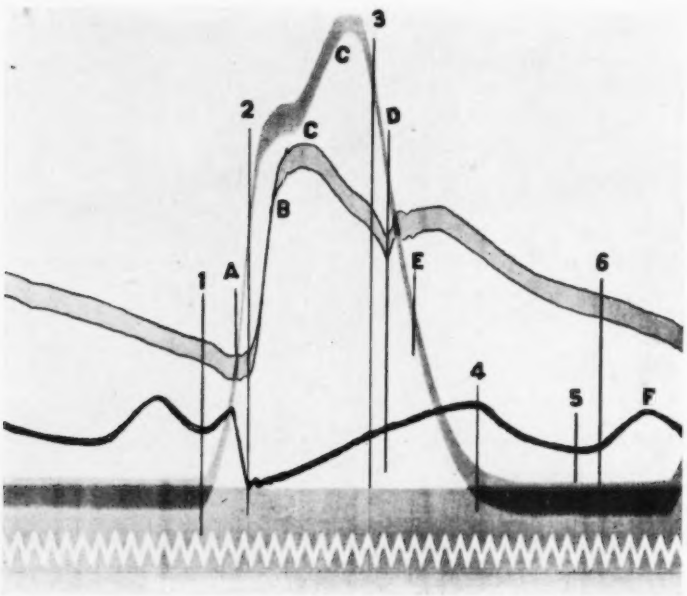

Fig. 2. Synchronous records of aortic left auricular and left ventricular pressures. Letters same as in figure 1.

of the auricular pressure curves such as are shown in figures 1 and 2, indicates that the intra-auricular pressure rises synchronously with or very slightly after the first elevation of intraventricular pressure. These and similar elevations shown also in the published curves of Piper (5), as well as in those of Garten and Weber (18), might readily be accounted for by such a regurgitation. Close inspection of the intraventricular pressure curves also indicates that the pressure increases in two stages, first slowly, *1-a*, then suddenly changing to a steeper

incline, *a-2*. This change in the rate of tension development may, of course, be attributed to various causes. Thus, de Heer (12) points out that in such a gradual beginning, it resembles the isometric tension curve of a skeletal muscle, and believes that it represents the time required for the development of a concerted muscular contraction. Fahr (19), without much warrant, interprets a similar rise in Garten's curves as due to the earlier contraction of the papillary muscles. Piper (5) explains this rise as due to a loss of energy during the closure of the a-v valves, and is inclined to believe that a point somewhere near *1-a* represents the moment of complete closure of the a-v valves. The further observation reported by Dean and myself (20) that the amplitude of the first heart sound increases at this point would favor such an interpretation.

The bulk of recent work tends to favor the idea that final and complete closure of the a-v valves is not produced until some elevation of intraventricular pressure has taken place. It may at once be pointed out, however, that this does not preclude the incorporation of this short interval in the isometric contraction phase for, during this interval of time, the valves are undoubtedly in the process of closure and the orifice must be exceedingly small. Consequently, during this brief interval, the ventricular contraction must be so nearly isometric in character as to make it undesirable to further subdivide this phase of contraction.

Having settled upon the initial elevation of intraventricular pressure as the beginning of the isometric phase, we may consider the other criteria that correspond to this point. Wiggers and Dean (20) have shown that the *first* maximal vibration of the first heart sound begins synchronously with the first elevation of the pressure rise. Consequently, this point may be taken as coincident with the elevation of intraventricular pressure and the beginning of the isometric phase. Is the beginning of the isometric phase also indicated on the arterial pressure records from the aorta and central arteries? In a detailed analysis of the central arterial pulse recorded from the subclavian or innominate artery, Frank (7) observed that a small preliminary vibration (2te Vorschwingung), such as is marked *C-D* in figure 3, usually precedes the primary rise in pressure. This wave he interpreted as occurring during the isometric phase. Subsequent work, however, indicates that the beginning of this wave does not definitely mark the very onset of systole. In the pulmonary arterial pressure curves the writer (2) usually found two such vibrations and similar double vibrations are shown in the arterial pressure curves published by Piper (5)

and Garten (6). These investigators, moreover, showed that such double vibrations begin a few σ after the beginning of ventricular contraction, relations that are confirmed in my tracings (cf. fig. 2). Frank further observed that when arterial pressure is low, this preliminary vibration is preceded by a negative dip similar to the depression *B-C* shown in figure 3. Such a depression is quite constantly present in pulmonary arterial pressure curves and not infrequently in optical arterial pulse tracings taken from man. These experiments indicate that this negative depression, rather than the positive wave following, coincides with the beginning of the intraventricular pressure rise. When present, this depression may therefore be taken as the beginning of systole. Unfortunately, however, it is so inconstant and its beginning so difficult to determine, that such tracings can not be relied upon in calculating the beginning of the isometric contraction phase.

The phase of isometric contraction ends with the beginning of the ejection phases. This point is indicated definitely by the sharp rise of aortic pressure (figs. 1 and 2) but its location on the ventricular pressure curves has been much discussed. According to Piper's interpretation (5), the intraventricular pressure curve shows, at the moment of ejection, a small notch topping the sharp rise of intraventricular pressure; while C. Tigerstedt (2) and Garten (6) both believe that this notch, when it occurs, is synchronous with the primary wave of the aortic pulse. My own results are in agreement with those of the latter investigators and indicate that the transition from the isometric to the ejection phases occurs without interruption of the intraventricular pressure rise or is indicated at most by a very slight change in the gradient (e.g., fig. 2). It follows that the intraventricular pressure curves, on the whole, do not show a sufficiently clear criterion for determining the end of the isometric contraction phase. Nor do minor variations in intra-auricular pressure bear a constant relation to the end of this phase. Thus, in figure 2, the sudden drop of intra-auricular pressure occurs precisely with the rise of aortic pressure, but in figure 3 it appears to occur somewhat earlier.

Conclusion: The onset of the isometric contraction phase may be accurately obtained from the initial rise of intraventricular pressure, from the onset of the first sound vibration, and sometimes though less surely, from a depression preceding the initial vibration in the arterial pressure curves; the end of the isometric contraction phase can be determined only by the rise of aortic pressure.

The ejection phase and its subdivision. The ejection phase obviously begins where the isometric contraction phase ends. As a matter of convenience, Hürthle placed its end at the point where the semilunar valves have closed, which would be at the bottom of the incisura of the intra-arterial pressure curve (figs. 1 and 2, *D*). Inasmuch as the beginning of a muscular relaxation is definitely indicated by the beginning of the incisura, it seems preferable to consider this the end of the ejection phase. Accordingly it is possible, as in figures 1 and 2, to

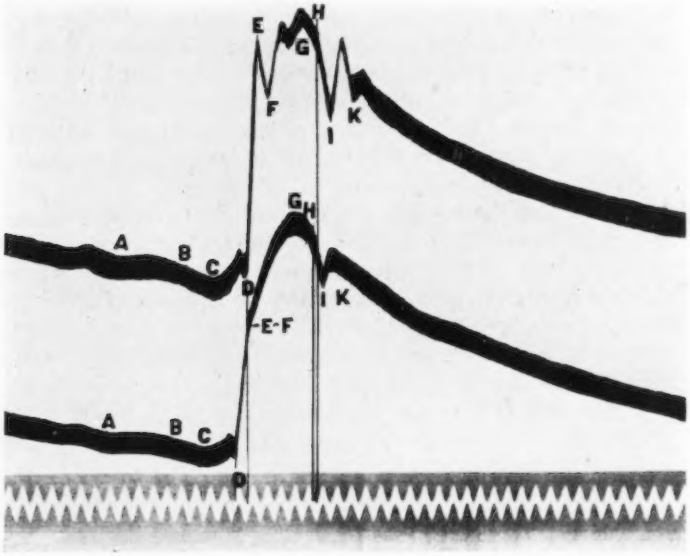

Fig. 3. Synchronous records of pressures in aorta near semilunar valves (lower) and in innominate artery (upper). Showing the addition of systolic vibrations in central arteries. Letters referred to in text.

include the ejection phase by the lines *2* and *3* and consider the pressure variations in the cardiac chambers and large arteries.

The optical tracings recorded by O. Frank (7) from the subclavian and innominate arteries show several variations during the ejection phase (cf. also fig. 3). The pressure change is initiated by a large primary vibration, *D E F*, reaching a prominent peak. This is followed by a more gradual rise to a summit, *G*, and lastly by a gradual decline to *H*. In the root of the aorta, near the semilunar valves,

these variations are all present except the pronounced primary vibration, *D E F*, which is much reduced, according to the records published by Piper (5), C. Tigerstedt (2) and Garten (6). That this is not determined by experimental conditions is clearly proven by synchronous records of the aortic and subclavian pulse, a specimen of which is shown in figure 3. It is quite apparent that this vibration is intensified as the rapid pressure change is transmitted to the aortic branches. The summit of the aortic pressure curve (figs. 1, 2 and 3, *F*) may come early or late in the ejection phase, the time depending, according to O. Frank, on how rapidly a balance is struck between systolic ejection and the peripheral flow from the arterial system. Whenever, therefore, the arterial pressure does not continue to increase until the end of systole, the assumption may safely be made that the rate of ventricular ejection has decreased and the summit may be used as the point separating the early phase of maximal ejection from the later phase of reduced ejection.

Before discussing the relation this bears to the mode of ventricular contraction, it is necessary to briefly consider the changes of intraventricular tension during these phases. Inasmuch as aorta and ventricle are a common cavity during the entire phase of ejection, it may be anticipated, on *a priori* considerations, that the contours of the ventricular and aortic pressure curves are similar and that the times of their summits coincide. This is frequently the case, as is shown in figure 1, and also in many published tracings of C. Tigerstedt (2) and Garten (6). It was therefore quite startling to find that in fully 50 per cent of my tracings such correspondence does not obtain. Figure 2 is really used as an extreme illustration of such discrepancy in the two curves. Obviously, the pressure summit, *C*, is reached quite early in the aortic curve, while it is greatly delayed in the intraventricular curve. In fact, while the aortic pressure is declining, the intraventricular pressure is rising. The suggestion has therefore occurred to me that, under certain experimental conditions of the circulation, a functional stenosis, due to the systolic approximation of the semilunar valves, may supervene to produce such effects. Less blood entering the aorta would account for the aortic pressure decline; an increased retention would, likewise, explain the simultaneous elevation of intraventricular tension. Attention is directed to these instances in order to impress the fact that a reduced discharge of the ventricle toward the end of systole is not necessarily due to a reduction in contractile energy or to an inadequate volume of blood for expulsion but may possibly also arise from an accidental functional valvular phenomenon.

Conclusion: The ejection of blood may be considered as occurring in two phases, the maximum ejection phase and the reduced ejection phase. The time occupied by these phases may be computed most accurately from the aortic pressure curves, the maximum ejection phase extending from the beginning of the steep pressure increase in the aorta to the summit of the curve; the reduced ejection phase extending from the latter point to the beginning of the incisura.

The early diastolic fall in pressure and its subdivision. With the beginning of ventricular relaxation, several consecutive events follow in rapid sequence: the semilunar valves close, the a-v valves open and then blood rushes into the ventricle. When the latter event begins, the early diastolic fall in pressure is nearly completed. As this inflow of blood is definitely accompanied by a fall of intra-auricular pressure, we may consider the lines *3–4* (figs. 1 and 2) as limiting this phase.

In marking the beginning of this phase as taking place at the moment when systole ceases (e.g., *3*, figs. 1 and 2), we include the time occupied by the closure of the semilunar valves, *3-d*. As already pointed out, Hürthle and many who have followed him include this interval in the period of systole. There can be no doubt, however, that ventricular contraction ceases at *3* and that strictly this is not a post-systolic phase. Is it, however, a proto-diastolic event? Has the left ventricle actually begun to relax? What actually happens is this: with the cessation of ventricular contraction at *3*, the pressure at once falls in the ventricle and communicating aorta. The backward movement of blood, indicated in the aortic incisura, probably brings into apposition the semilunar valves which have already floated toward a position of closure. Not until such closure has been effected, however, does a steep decline of intraventricular pressure, such as one might logically associate with a relaxation process in muscle, take place. It is quite probable therefore that the passing of the ventricle from a state of systole to that of diastole is not a momentary event but is represented rather by this time interval required for the closure of the semilunar valves. In this sense the interval belongs, strictly speaking, neither to the period of systole nor to that of diastole. Since we would be unwarranted on the basis of such a hypothetical analysis and its extremely short duration in considering this as an intermediary period of the ventricular cycle, we are forced to add it either to the period of systole or to that of diastole. The former has usually been done. Since all evidence points to the end of muscular contraction previous to this point, however, and since the phase of diastole already includes

other events than those associated with actual relaxation processes in the muscle, I believe it most logical to consider this as a proto-diastolic rather than a post-systolic event.

As already indicated, the duration of the proto-diastolic phase is measured by the time required for the arterial fall in pressure designated as the incisura *3-d*. A similar drop of pressure may be present in the intraventricular pressure curve. Here, however, the end alone is distinct, the beginning being, as a rule, difficult to place. The intra-auricular pressure curve shows no landmarks by which the duration of this phase can be directly determined.

The time interval existing between the complete closure of the semilunar valves and the opening of the a-v valves, *D-4*, represents the isometric relaxation phase. It is determined most accurately from the combined aortic and auricular pressure curves. During this phase of isometric relaxation, the pressure at first falls abruptly (fig. 1, *D-E*) and then more gradually (fig. 1, *E-4*). Attention has been directed to this change in gradient by Garten (6), who offers no explanation as to its cause. In previous publications I have interpreted the change in gradient as coincident with the inflow of blood from the auricle, i.e., have interpreted this to represent the end of the isometric relaxation phase and the beginning of the rapid diastolic inflow phase. On the basis of Piper's curves (5) and also my own, this interpretation appears incorrect. Obviously, a great transfer of blood from the ventricle to the auricle does not occur until the auricular pressure drops, a short time after (4). Tachograms of the ventricle recently reported by Straub (13), (21) led him to believe that about this time the a-v valves bulge more rapidly toward the ventricle previous to opening. This may be the explanation of the change in pressure gradient. The end of the isometric relaxation phase is therefore not clearly indicated on the intraventricular pressure curve itself.

Conclusion: The early fall of ventricular pressure constitutes two diastolic phases: a proto-diastolic phase, the length of which is indicated by the duration of the incisura of the arterial pressure curve, and an isometric relaxation phase extending from the bottom of the incisura to the fall of auricular pressure coincident with the onset of ventricular filling.

The phases of rapid diastolic inflow and diastasis. According to the ventricular volume curves of Henderson (11), the ventricles, under normal conditions of venous pressure, fill within a short time interval after opening of the a-v valves. If the cycle is long, this filling comes

to an abrupt end due to an equalization of auricular and ventricular pressures. The first stage may well be designated as the phase of rapid inflow; the second, during which a gradual filling occurs, as *diastasis*. Naturally, as Henderson and his collaborators point out, the stage of diastasis is non-existent whenever the total period of diastole does not exceed the time taken for the rapid inflow. Is this subdivision of diastolic inflow justifiable? Not all physiologists hold that the ventricle fills in this manner but, on the contrary, believe that approximately the same rate of ventricular inflow persists throughout diastole. This idea is based on the interpretation of ventricular volume curves recorded by Straub (21), Patterson, Piper and Starling (9), Socin (22) and others. It is not proper at this time to enter into a discussion as to the cause of these discrepancies. We may, however, at present approach the subject from another angle, viz., the evidence supplied by synchronous pressure curves. If a period of stasis normally supervenes in long cycles, we may anticipate that the intra-auricular pressure recorded by sensitive manometers will rise subsequent to its diastolic decline, whereas if a rapid inflow of blood into the ventricles continues throughout diastole, no such increase should be observed. That the latter condition is frequently found is apparent from tracings published by Piper and also by Garten. In my own tracings about 28 per cent of the left auricular pressure curves showed a definite increase such as is evident in figure 1. In these cases, at least, we must infer a distinct phase of diastasis. It is possible to interpret the failure of the auricular pressure rise in the other 72 per cent of cases as showing that ventricular inflow into the ventricles continues with sufficient rapidity so that no rise of auricular pressure takes place. Even if such a phase is present only in a minority of experiments, it seems desirable to retain this subdivision of diastole into phases of *rapid inflow* and *diastasis*.

Conclusion: Since the ventricular inflow in a certain proportion of cases is sufficiently interfered with to cause an elevation of auricular pressure, it seems preferable to subdivide the filling periods of the ventricle into a phase of rapid inflow extending from the fall of auricular to the subsequent rise of auricular pressure (i.e., *4–5*) and to consider the remainder of diastole up to the beginning of auricular systole, *5–6*, as a phase of diastasis.

The "auricular-systole" phase of diastole. Considerable difference of opinion has also developed as to the efficacy of auricular systole in filling the ventricles. Henderson (11) believes that the auricular contraction contributes only an insignificant increment, while Straub (13),

(21), Patterson, Piper and Starling (9), as well as Gesell (15) hold that ventricular filling is helped in this way. As a more comprehensive analysis of this question is anticipated, we shall restrict our present evidence to the pressure curves. If auricular systole injects a considerable quantity of blood into the ventricle, we may anticipate an elevation of intraventricular pressure. As Frank (7) pointed out, such a wave is frequently found in the aortic pressure curve which he interprets as a transmission of a similar intraventricular variation. Previously published optical curves of different investigators give instances in which such an auricular wave is present in the ventricle. In my large collection of normal records it is present in only 13 per cent. In many cases, as shown in figure 1, the wave may be entirely absent from the intraventricular curve yet distinctly indicated by the intra-aortic curve, which makes it probable that Frank's explanation of the latter is incorrect and that it owes its origin to a direct communication of pressure from the auricle. Again, it is desirable to take cognizance of such a phasic event in the cardiac cycle since it is present in some cases. Such recognition requires that we go further, however. Auricular systole is capable of exerting a dynamic effect on the ventricle—either increasing its volume or elevating the initial tension to which fibers are submitted—only so long as the intra-auricular pressure continues to rise. In a previous communication (23) I have pointed out that auricular pressure rises only during the early half of its systole and that, before systole is over, it may have declined to the pressure level existing before its onset. This primary elevation of auricular pressure alone causes a flow of blood ventricleward, while during the decline of auricular pressure due to the passing off of certain fractionate contractions blood actually enters the auricle from the veins. We may therefore divide auricular systole into an early Dynamic Interval and an Inflow Phase.

THE DURATION OF THE CONSECUTIVE PHASES OF THE CARDIAC CYCLE IN THE DOG

The duration of each successive phase of the cardiac cycle of normal dogs was established in 38 carefully controlled experiments. Two classes of these experiments were carried out, viz., *a*, those in which the animal was placed under light morphine and chloretone anesthesia and the thoracic cavity left intact; and *b*, those in which the heart was exposed but the pericardium and its attachments left intact. In the former experiments, right auricular and subclavian pressures were

optically recorded together with the heart sounds; in the latter, curves of left auricular, left ventricular and aortic pressures were taken. From these records the successive phases summarized in the diagram of figure 4, were calculated according to the criteria above analyzed.

The margin of variation in consecutive heart beats. When the duration of the separate phases of systole and diastole are estimated by accurate methods, small variations in the duration of many phases occur from beat to beat. These are attributable partly to normal modifications of the heart beat, partly perhaps to unavoidable errors or personal factors introduced in measuring curves. It is therefore necessary for any experimenter to evaluate the combined factors before lending significance to variations which may occur under modified conditions of the circulation.

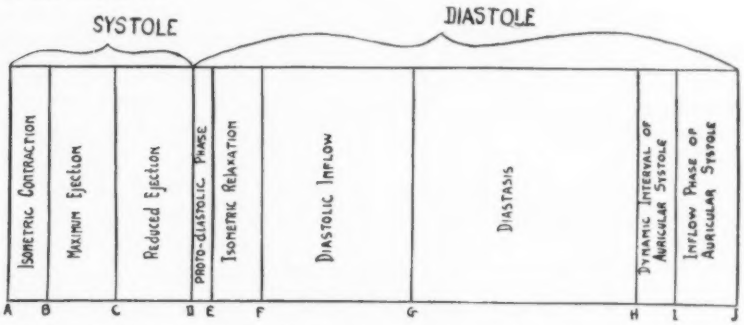

Fig. 4. Scheme showing consecutive phases of cardiac cycle

For this reason the duration of each successive phase in each of 15 consecutive cardiac cycles was first personally calculated and tabulated. From 38 of these tabulations a second table was made which showed the margin of variation that existed in each phase (table 1). A study of such tables containing values for about 1000 cardiac cycles showed the following *maximal variations* in 15 consecutive cycles of normal anesthetized animals; the actual variations in most series of heart beats being of course very much smaller: Isometric contraction phase, 0.008 second; maximum ejection phase, 0.01 second; reduced ejection phase, 0.022 second; proto-diastolic phase, 0.01 second; isometric relaxation phase, 0.01 second; early diastolic inflow phase, 0.045 second; diastasis phase, variable; auricular systole, 0.027 second (table 1). Changes in the duration of any phase during experimental procedures

in excess of these variations may therefore be safely considered as *prima facie* evidence of an alteration arising in consequence of the altered circulatory conditions.

The influence of opening the thorax and of cardiac exposure. In view of the fact that the cardio-dynamics are certainly altered in many

TABLE 1

The duration of consecutive phases of the cardiac cycle in dogs

	ISOMETRIC CONTRACTION	MAXIMUM EJECTION	REDUCED EJECTION	TOTAL SYSTOLE	PROTO-DIASTOLE	ISOMETRIC RELAXATION	RAPID INFLOW	DIASTASIS	AURICULAR SYSTOLE	TOTAL DIASTOLE
A. In exposed hearts (22 experiments)										
Range	0.042–0.078	0.050–0.130	0.031–0.142	0.149–0.305	0.012–0.038	0.050–0.112	0.022–0.104	0.000–0.246	0.044–0.078	0.184–0.494
Average (when possible)	0.045–0.050				0.025	0.060–0.070	0.080		0.070	
Variation*	0.000–0.006	0.003–0.010	0.003–0.022		0.001–0.010	0.000–0.010	0.001–0.009			
B. In closed chest experiments (16 experiments)										
Range	0.038–0.054	0.050–0.110	0.063–0.144	0.148–0.260	0.015–0.035	0.04 –0.090	0.040–0.130	0.000–0.540	0.062–0.120	0.184–0.496
Average (when possible)	0.048–0.050				0.022	0.048–0.050	0.045–0.060		0.085	
Variation*	0.000–0.008	0.000–0.010	0.000–0.012		0.000–0.005	0.001–0.010	0.000–0.045		0.027	

*The two figures refer to the least and greatest variations found in 15 consecutive cycles taken in the same animal.

respects when the chest is opened, it becomes necessary to analyze what effect such experimental procedures exert on the lengths of the successive phases of the cardiac cycle. The results alluded to above and summarized in table 1 were obtained from 22 animals in which the thorax was left intact and from 16 animals in which the heart was exposed. The two series of results show a fortunate correspondence

as to ranges both of heart rate and lengths of systole and diastole, making it possible to compare data as to variations of the smaller phases.

Considering the results, phase by phase, it is evident that the isometric contraction phase in the case of exposed hearts shows practically the same variations as that of the enclosed heart. The durations of the maximum ejection phase and reduced ejection phase, both absolute and relative, show variations, however, that are distinctly greater in the exposed heart. This indicates that the adaptation of the ejection rate to the peripheral resistance is altered to varying degrees in different operated animals. This is precisely what might be expected for the amount of blood lost in opening the thorax, and possibly also the early vascular reactions of shock incident to the operative procedures is naturally variable in the case of different animals. Furthermore, the value of the respiratory pressor factor (i.e., the assistance offered by respiratory movements to the filling and emptying of the heart) is not constant in different animals, consequently its elimination may operate to affect the duration of the phases of maximum ejection more in some animals than in others.

Passing to the diastolic phases, we note a remarkable correspondence in the duration of the proto-diastolic phases, which it should be recalled represent the times required for the semilunar valves to float into apposition. If anything, this phase is slightly greater in the case of the exposed heart. The predominant duration of the isometric relaxation phase is longer in the exposed heart by fully 0.02 second. The phase of early diastolic inflow varies greatly both in closed and open chest experiments, but the predominant length is again longer in the case of the exposed heart. Whether this indicates that the negative intrathoracic pressure assists the isometric relaxation and rate of rapid inflow when the chest is intact can not be definitely stated. The fact must be borne in mind that the data from open chest experiments were derived by the aid of left auricular tracings, those from closed chest experiments from right auricular tracings. We are not yet in a position to state conclusively that the two ventricles always and necessarily begin to fill at the same time.

In considering the great variation in the duration of the early diastolic inflow phase, we must, of course, consider the possibility that this phase might have been prematurely terminated in some cases by the onset of the next systole. In other words, variations in this phase are only of vital significance when the heart is slow and a phase of diastasis can

exist. It was found in the 38 experiment studies that there were 14 cases in which a possible diastasis phase could exist. In 12, or 85 per cent, a distinct indication of a diastasis phase, such as is shown in figure 1, was shown. In only two cases the fall of auricular and presumably a rapid rate of ventricular inflow continued until the onset of the next auricular systole. In these 12 experiments in which the evidence of a diastasis phase is present, the early diastolic inflow phase varies from 0.044 to 0.13 second, the prevailing period in closed chest experiments being 0.045 to 0.06 second. In the open chest experiments the prevailing duration is somewhat longer, i.e., approximately 0.088 second. We may therefore infer that 0.045 second is the very minimum time interval during which the heart can fill rapidly after opening of the a-v valves and that in many cases this interval is much longer.

TABLE 2

Comparative results as to duration of diastolic phases

PHASES	HENDERSON (11)	DE HEER (12)	AUTHOR'S RESULTS	
			Open chest	Closed chest
Proto-diastolic plus				
A. Isometric relaxation	0.077	0.025	0.085	0.072
B. Rapid inflow	0.052	0.135	0.08	0.06
Total ($A + B$)	0.129	0.15	0.165	0.132
Auricular systole	0.110	0.085	0.07	0.08

Physiological significance of results. One of the mooted questions of cardiodynamics is that of the manner in which diastolic filling of the ventricles takes place. The ventricular volume curves of Henderson (11) and de Heer (12) indicate that, after short proto-diastolic and isometric relaxation phases, ventricular filling follows rapidly. After this the inflow rate is greatly reduced, i.e., a period of diastasis supervenes which continues until the next auricular systole follows. In the following table is given a comparison of the data calculated from the typical reconstructed volume curves of Henderson (11) and de Heer (12) together with some actual figures obtained from these experiments as to the relative lengths of the diastolic phases exclusive of diastasis (table 2).

These comparisons render it obvious that (with the exception of a wrong calculation by de Heer for the proto-diastolic and isometric relaxation periods, which correspondingly lengthens the early diastolic inflow phase) the results are in as close agreement as could logically be

expected. This is of significance for it indicates that, as far as temporal relations are concerned, the heart relieved of its pericardial support and enclosed within a plethysmograph relaxes and fills like the heart in the intact chest.

As previously stated, the view that the heart fills as indicated by Henderson and his collaborators has not been supported by other investigators who believe that filling continues rapidly throughout diastole, and that no phase of diminished inflow or diastasis exists. Henderson has repeatedly pointed out, by clear and emphatic logic, that the failure of such records to evidence a diastasis phase is due to a rapid heart rate and the consequent shortening of the total diastolic length. On the basis of my results we may calculate how short total diastole must become in order to have the phase of diastasis disappear entirely. Let us add together what, on the basis of my results, must admittedly be conservative intervals for the following diastolic events:

	Second
(a) Proto-diastolic phase	0.022
(b) Isometric relaxation phase	0.05
(c) Early diastolic inflow phase	0.06
(d) Auricular systole	0.085
Total	0.217

It is obvious that unless diastole exceeds 0.217 second, no phase of diastasis is possible; if it is shorter, the early diastolic inflow phase must also be encroached upon by auricular systole.

Let us, however, make another calculation of the following events:

	Second
Proto-diastolic phase	0.022
Isometric relaxation phase	0.05
Auricular systole	0.085
Total	0.157

It is obvious that the phase of early diastolic filling must be entirely absent when total diastole is reduced to about 0.16 second, consequently ventricular filling then occurs only during auricular systole. Owing to the fact that systole and diastole vary independently in length, it is not possible, I believe, to accurately translate these figures into terms of heart rate. It is probable, however, that whenever the heart rate increases to 180, auricular contractions come during the early diastolic inflow phase, while at the rate of 200, ventricular filling must come

entirely during auricular contraction. I take this occasion to reëmphasize by definite figures what Henderson and his collaborators have so clearly demonstrated by the use of volume curves, because it seems difficult to drive home the idea that such records as are obtained from rapid hearts can supply no critical proof of what obtains in the filling of hearts at rates that may be regarded as quite normal for man.

SUMMARY

An analysis of optical pressure curves from a total of over 200 dogs, in 38 of which special pains were taken to maintain normal conditions, leads to the following interpretation of the consecutive phases of the ventricular cycle:

1. At the beginning of ventricular systole, the a-v valves have been partly floated into apposition, probably in consequence of the sudden cessation of a jet when the peak of the intra-auricular pressure curve is reached about the middle of auricular systole. The first elevation of intraventricular pressure firmly closes these valves and the ventricle then contracts absolutely isometrically. *This first phase of ventricular systole extending from the beginning of the pressure rise until the opening of the semilunar valves is preferably considered as the isometric contraction phase.* The predominant durations of this phase range from 0.048 to 0.05 second when the chest is intact, and from 0.045 to 0.05 second when the heart is exposed.

2. As soon as intraventricular exceeds intra-aortic pressure, the semilunar valves open and a comparatively large volume of blood is ejected. As long as the volume ejected remains greater than the outflow from the peripheral arterioles, the aortic pressure continues to rise. This marks a *second phase of maximum ejection.* As soon, however, as the systolic ejection decreases enough so that it no longer equals the peripheral outflow, then the aortic pressure begins to decline. This *third phase* when present may be designated as the phase of *reduced ejection.* This terminates the period of systole. The absolute and relative durations of these phases vary considerably, the greatest variations in closed chest experiments being 0.05 to 0.11 second for the maximum ejection phase and 0.063 to 0.144 second for the reduced ejection phases.

3. When ventricular relaxation begins, aorta and ventricles are still in communication. The first event, viz., the closing of the semilunar valves, is signalled by a sharp drop in aortic and intraventricular pressure, designated as the incisura. This marks the *fourth* or *proto-diastolic*

phase. This phase is relatively constant averaging 0.022 second in closed chest experiments and 0.025 second when the heart is exposed.

4. Following closure of the semilunar valves and until the a-v valves have opened, the ventricle relaxes without any flow of blood either from or into its cavity. This marks the *fifth phase* or that of *isometric relaxation*. The predominant duration of this phase in exposed hearts is 0.06 to 0.07 second but is predominantly shorter in animals with thorax intact, ranging from 0.048 to 0.05 second.

5. With the opening of the a-v valves and until either an equalization of pressure between auricle and ventricle has taken place or a subsequent systole interrupts the filling, a rapid filling of the ventricles takes place. This is the *sixth phase*, conveniently designated as the *rapid inflow phase*. This phase averages from 0.048 to 0.05 second in closed chest experiments and from 0.06 to 0.07 second in exposed hearts.

6. In long cycles and when the auricular pressure is normal, a period of reduced filling obtains which may be designated, after Henderson's suggestion, as the *phase of diastasis*. Its duration is obviously dependent on the length of total diastole.

7. Finally there may be added an *eighth phase* during which the dynamic interval of auricular systole affects the filling or pressure of the ventricles. This does not continue until the end of auricular systole, however, but a terminal phase of auricular systole in which no dynamic effect can be exerted exists before the entire cycle is completed. The predominant durations of the total phase of auricular systole average 0.07 second in exposed hearts and 0.085 second in hearts enclosed within the thorax.

A pictorial summary of these dynamic events occurring during ventricular systole and diastole is schematically indicated in figure 4.

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STUDIES ON THE CONSECUTIVE PHASES OF THE CARDIAC CYCLE

II. The Laws Governing the Relative Durations of Ventricular Systole and Diastole

CARL J. WIGGERS

From the Physiological Laboratory, Western Reserve University, School of Medicine, Cleveland, Ohio

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While the relation existing between the lengths of systole and diastole have been quite extensively studied under a variety of conditions, both in animals and man, the fundamental laws which determine the extent and direction of these variations under different circulatory conditions have not been clearly formulated.

Perhaps the most definite existing basis upon which to attempt such a formulation of governing laws rests upon the interpretation given the ventricular volume curves by Henderson and his collaborators (1). These investigators, it will be recalled, pointed out that under normal conditions of venous pressure both ventricular filling and discharge occur after a constant pattern, exemplified by a record of the ventricular volume changes. According to their interpretation, the extent of ventricular filling and discharge under normal conditions can be determined solely by changes in the length of preceding diastoles. It was recently pointed out by Katz and myself (2) that it becomes a necessary corollary of such a conception that the durations of systole and diastole at any heart rate must bear a fixed relation to each other, which relation we believe it is possible to derive from an animal and express in a curve form. Actual experimental observations showed, however, that these relations are not maintained when the heart is accelerated either by stimulation of the accelerator nerves or after the administration of adrenalin. Subsequently Katz (3) also directed attention to the fact that during the course of vagal slowing or during subsequent recovery from such slowing, these relations do not hold good. Our former observations may be interpreted in part at least as indicating a specific effect of the accelerator nerves on the ventricles,

but the latter effect certainly is more probably interpreted as, in some way, associated with alterations either in venous pressure or arterial resistance (3). That changes in venous return or arterial resistance may have a direct determining effect on the length of systole is also indicated in several reports from other laboratories. Thus Lombard and Cope (4), finding that the systoles of the left ventricle are longer in the sitting and lying down position than in the standing position, suggested that the greater return of venous blood may possibly act to lengthen the duration of systole in man. Such a lengthening effect of increased venous return on systole was not demonstrated, however, in the experiments of Patterson, Piper and Starling (5) who worked with the heart of a "heart-lung preparation." On the other hand, these investigators observed that an increased arterial resistance consistently lengthens the contraction phase.

In view of the practical bearing that this problem has on the interpretation of many dynamic reactions, and in view also of the apparent discrepancies suggested in the recent work, it seemed appropriate to submit this question to a more fundamental analysis. This could only be accomplished, however, by determining the effects of different procedures on each of the consecutive subdivisions of the cardiac cycle.

METHODS AND PROCEDURES

Since, under physiological as well as pathological and pharmacodynamic conditions, three variables may possibly affect the durations of the consecutive phases of systole and diastole, viz., changes in heart rate, venous return and arterial resistance, experiments were instituted to test the reaction of these factors, when operating singly or combined. In order to do this, intact animals were used exclusively because, on mature reflection, it was felt that the use of a heart-lung preparation introduced fully as many uncontrollable variables as the employment of the intact animals, and would moreover be apt to show what *can* take place rather than what *does occur* in the body.[1]

In order to study the effects produced by variations in heart rate, the vagus nerves were divided or stimulated directly. In order to prevent changes in rate when arterial resistance and venous inflow were altered, it was necessary to divide both vagi nerves. The volume of venous return was reduced by compression of the inferior vena cava

[1] For a full discussion of this problem, consult Wiggers, Harvey Lecture published in the Archives of Internal Medicine 1921, xxvii, 475.

and augmented by a graded inflow of saline solution. In such cases records of the resulting effective venous pressure rather than of the amount injected were kept. Arterial resistance was increased by the production of peripheral vasoconstriction and also by mechanical compression of the abdominal or ascending portions of the aorta. Whenever possible, experiments were carried out both on animals with thorax opened and on those in which the chest remained intact.

THE INFLUENCE OF INCREASING THE VOLUME OF VENOUS RETURN

In interpreting the uncomplicated effect of an augmentation of venous return occasioned by saline infusion, it was important that the venous pressure should not at the outset be below normal. Only those experiments in which an effective right auricular pressure above 55 mm. saline solution existed are therefore included in this analysis. It is also important that concomitant changes in heart rate or arterial resistance should preferably not occur at all or, if taking place, that they be taken into account. While, in many animals, saline infusion caused no appreciable change in heart rate when both vagi had been severed, minor variations frequently occurred. Their possible influence on the duration of systolic phases, as will appear in later discussion, could always be evaluated by bearing in mind that slowing alone has a natural tendency to lengthen systole; acceleration, the reverse effect. Arterial resistance always increased to some extent but, owing to the slow rate of inflow and the reduced viscosity of the blood, systemic diastolic pressure was not markedly altered (cf. table 1). In fact, it was shown in control experiments that a similar degree of resistance increase was either without effect on systole or tended to operate in an opposite manner. It is therefore possible to clearly analyze the specific effects resulting from an increased venous return.

Effect on relative duration of systole and diastole. If, during the course of a venous infusion, the heart rate is counted it is usually found that in spite of vagotomy a slight retardation of the beat takes place, and that this may progress as the infusion continues. Comparison of the periods of systole and diastole show, however, that the slowing is of an entirely different order than when the vagus is stimulated; it is systole rather than diastole that lengthens. The sequence of these changes may be followed by data taken from experiment 231, x, which are incorporated in table 1. The periods obtaining under normal conditions are shown as *a*. Very soon after infusion started, the heart slowed, *b*, due to an increase both in the length of systole and diastole.

TABLE 1

The influence of increased venous return on the duration of consecutive phases of systole and diastole

EXPERIMENT NO.	SYSTOLIC PHASES				DIASTOLIC PHASES					DIASTOLIC ARTERIAL PRESSURE	INITIAL PRESSURE (MM. Hg)
	Isometric contraction	Maximum ejection	Reduced ejection	Total systole	Proto-diastole	Isometric relaxation	Rapid inflow	Diastasis	Total diastole		
231, X											
a	0.055–0.058	0.062–0.080	0.060–0.070	0.185–0.208	0.020–0.030	0.040–0.047	0.047–0.055		0.222–0.234	68	4.2
†b	0.045–0.055	0.070–0.080	0.116–0.125	0.240–0.246	0.020–0.024	0.050–0.058	0.070–0.078	0.024–0.036	0.278–0.284	68	4.8
†c	0.040–0.047	0.068–0.070	0.143–0.155	0.253–0.270	0.020–0.030	0.060–0.070	0.058–0.068		0.230–0.233	70	9.1
†d	0.045	0.074–0.080	0.105–0.112	0.229–0.232	0.020–0.024	0.049–0.058	? –0.055		0.208–0.219	72	7.9
230, XIV											
a	0.052–0.057	0.065–0.070	0.073–0.077	0.190–0.200	0.025–0.032	0.040–0.045	0.032–0.050		0.175–0.192	44	4.8
*a′	0.050–0.052	0.100–0.102	0.070–0.078	0.222–0.223	0.026–0.035	0.040–0.046	0.040–0.048	0.272–0.285	0.470–0.483	33	7.1
†b	0.050–0.053	0.055	0.096–0.097	0.201–0.205	0.028–0.030	0.040–0.044	0.036–0.038		0.198–0.202	43	5.2
†d	0.043–0.050	0.080–0.088	0.09	0.220–0.223	0.03	0.045–0.052	0.040–0.042		0.193–0.197	42	6.9
*†e	0.048–0.053	0.106–0.140	0.098–0.118	0.250–0.295	0.025–0.035	0.050–0.053	0.040–0.06	0.162–0.560	0.303–0.787	33	9.2
†f	0.048–0.050	0.084–0.098	0.100–0.110	0.238–0.252	0.022–0.028	0.045–0.050	0.042–0.052		0.189–0.190	40	7.1
233, X											
a	0.050–0.052	0.063–0.067	0.118–0.120	0.234–0.237	0.020–0.026	0.040–0.048	0.064–0.075	0.155–0.169	0.400–0.412	42	5.3
†b	0.048–0.056	0.07	0.190–0.206	0.308–0.334	0.025–0.030	0.046–0.052	0.048–0.054	0.060–0.720	0.251–0.961	34–42	6.8
†c	0.048–0.054	0.062–0.064	0.140–0.170	0.250–0.280	0.030	0.030	0.048	0.290	0.468	38	8.3
†d	0.044–0.048	0.090–0.093	0.162–0.170	0.292–0.308	0.020–0.022	0.040–0.042	0.040–0.042	?	0.238–0.245	63	?
†e	0.040–0.045	0.090–0.098	0.170–0.172	0.300–0.315	0.028–0.030	0.040	0.045	0.02	0.223–0.228	45	10.3

* Indicates peripheral vagus stimulation.

† Indicates observations during increased venous return.

In *c*, the duration of diastole returned to normal but systole lengthened still more. After discontinuing infusion, as shown in *d*, diastole became shorter than it was at the start, but systole continued long. If the vagus nerves are stimulated at the time when systole has lengthened independent of diastole, a further lengthening of systole as well as diastole takes place. This is illustrated in experiment 230, xiv, table 1. The data shown as *a* and *a'* indicate control effects of vagus stimulation when conditions were normal just before infusion started. The maintenance of normal diastolic length and the gradual lengthening of systole during infusion are shown by *b* and *d*. Records from which these data were derived were taken early during the infusion process. When the vagus nerve was stimulated in addition and with the same strength of current as had previously been used, a very great slowing accompanied by a further lengthening of systole took place, *e*. After cessation of stimulation, the length of diastole returned to normal but systole remained lengthened, *f*.

Such results illustrate the response of a rapidly beating heart. It still remains to test the reaction of a heart normally beating at a rate which more nearly approximates that in man. Since it was important to avoid the influence of a varying vagal tonus, it was necessary to apply a continued electrical stimulus to the cut vagi and, during the course of such slowing, saline infusion was given. The results of such an experiment are shown in experiment 233, x, table 1. The data listed as *a* show the phasic relations existing during a mild stimulation of the left vagus which, in this case, produced a typical sinus slowing. While stimulation continued, infusion was started and during its continuance observations *b* and *c* were made. The data show without further comment that there is the same tendency for systole to lengthen independently of diastole.

Having shown that the duration of systole may increase independently of diastole when the return flow to the heart is increased, it remains to show that the effects were not primarily due to the increased arterial pressures against which the heart must expel its blood, especially so as Patterson, Piper and Starling found that such an increase of arterial resistance causes a lengthening of the contraction phase. In the first place, as shown by the diastolic pressure readings taken throughout these observations, the administration of saline infusion, as carried out in these experiments, does not cause any appreciable elevation of systemic pressure; in some cases a lengthening of systole occurs without any variation of pressure. When the blood pressure lowers,

as during vagus stimulation (e.g., exper. 230, xiv, *e*), systole lengthens still further and, as the heart subsequently accelerates (e.g., *f*), and before the blood pressure has returned to its former level, the systoles still remain long. It is possible, however, to reduce suddenly the arterial pressure during saline infusion, by opening up a carotid artery, thus allowing a profuse hemorrhage to take place for a short time. Data from such an experiment are illustrated in experiment 233, *e*. They show when compared with normal data, *d*, that systolic length is certainly not reduced, even though diastole may decrease slightly. As will be apparent later, such controls and others that have been employed might have been dispensed with entirely for, contrary to the findings of Patterson, Piper and Starling, an increased arterial resistance of even greater magnitude does not lengthen systole in the intact heart; but, on the contrary, tends to abbreviate it.

Influence on consecutive phases of systole. Tabulations of many experiments, of which those incorporated in table 1 are but specimen summaries, have shown that there is always a tendency for the isometric contraction phase to become abbreviated. Sometimes this abbreviation is marked, again it may be very slight. The following reductions have been noted in different experiments: 0.04 to 0.028; 0.043 to 0.035; 0.05 to 0.032; 0.052 to 0.033; 0.05 to 0.045; 0.055 to 0.052; 0.042 to 0.04; 0.048 to 0.046; 0.055 to 0.04; 0.058 to 0.047; 0.05 to 0.048; 0.051 to 0.056 (experimental increase); 0.052 to 0.048; 0.057 to 0.05. These observations bear out the results of Hürthle (6) and others who found that the duration of this phase is not related to the absolute diastolic pressure in the aorta but is determined rather by the difference between aortic and intraventricular pressures at the beginning of systole. Hürthle inclined to the opinion that the height of the initial pressure within the ventricle at the moment of systole is the fundamental factor. This interpretation is borne out by the results of this research (cf. table 1).

As the isometric contraction phase decreases in length during the continuance of an infusion, the combined phases of ejection lengthen. This indicates that the duration of the ejection process is adapted to the volume of blood which needs to be expelled. A study of the tables reveals no constancy as to whether the phase of maximal or reduced ejection is predominantly affected. As a rule, the latter phase is lengthened first and to greater degree; while the phase of maximal ejection does not increase until a considerable ventricular distention has supervened (cf. table 1). This is, naturally, of no fundamental

significance as bearing upon the nature of the ventricular behavior, but merely means that the flow of diluted blood from the peripheral arterial system keeps pace with the increased ventricular discharge early in systole. This, it may be noted, however, would not be the case if a secondary increase in arterial resistance were in any manner concerned with the increase in length of systole, and strengthens our belief that the rate of venous inflow is the direct factor involved.

There is apparently no doubt that an increased venous return and the consequently greater ventricular filling acts to shorten the isometric contraction phase and to lengthen the ejection phases, thereby prolonging systole as a whole. The question remains whether this is fundamentally due to an increase in diastolic volume (i.e., greater initial length) or to an increase in initial tension. The intraventricular changes occurring in those experiments of this series in which the chest had been opened have recently been reported and analyzed (7). They showed such clear and prompt correspondence between volume and initial pressure alterations that the conclusions seemed necessary that initial pressure changes were fundamentally responsible for such volume changes as occurred. Consequently, the conclusion is favored that the effects which the volume of venous return exerts on the phases of systole are fundamentally related to changes in initial intraventricular pressures.

Influence on consecutive phases of diastole. It is conceivable that the time required for the semilunar valves to close (i.e., the proto-diastolic phase) might be determined by the diastolic pressure existing in the aorta at this time. Apparently this interval is so short, however, and the pressure elevation so insignificant that no striking variations occur (cf. table 1). The data also reveal no marked changes in the duration of the isometric relaxation phase in the majority of cases. Occasionally, as shown in experiment 231, x, this phase lengthens by about 0.02 second. The cause of such an occasional prolongation is not clear. Suffice it to state that the causes which might be logically invoked to explain such a change do not appear to exist during saline infusion. They will be discussed more in detail later (cf. page 450).

Of greater importance as concerning the dynamics of the ventricle are the data relating to the length of the rapid inflow phase. The increased systolic discharge during saline infusion is necessarily due to a greater diastolic inflow. How is this brought about? Is the phase of rapid inflow prolonged, or does the greater filling occur in the same time interval? Tabulated data from these experiments fail to show that this phase is lengthened. It is true that when a rapid heart (in

which the phase of rapid inflow is abridged by a succeeding systole) slows down during the course of an infusion, this phase may be lengthened. This, however, is only a function of heart rate and would have occurred regardless of infusion. In cases in which the heart previous to infusion was sufficiently slow to permit of the existence of a diastasis phase, the phase of rapid inflow was certainly not lengthened (e.g., exper. 233, x, table 1).

THE INFLUENCE OF INCREASED ARTERIAL RESISTANCE

The arterial resistance against which blood must be expelled was augmented in three different ways, viz., *a*, by creating increased resistance in the terminal branches of the arterial tree through reflex vasoconstriction (stimulation of the central vagus nerve); *b*, by compressing the abdominal or lower thoracic aorta; and *c*, by compressing the ascending aorta near the semilunar valves (aortic stenosis). As before, the vagus nerves were cut, except as noted.

Effects on systole and diastole ratios. The net results of these experiments may first be summarized as follows: At constant heart rates, increasing the arterial resistance by vasoconstriction uniformly causes a decrease in the length of systole independent of changes in diastole. Similar changes usually follow compression of the abdominal or lower thoacic aorta. In a few cases the length of systole remains unchanged, however; in a few others it slightly lengthens. The former results, it may be pointed out, are contrary to, the latter in accord with the reactions reported by Patterson, Piper and Starling (5). During aortic stenosis systole invariably lengthens, thus confirming results already reported by de Heer (8).

These effects may be illustrated by reference to a few reactions tabulated in table 2. In experiment 219, ii, the effects of increased resistance following reflex vasoconstriction, *b*, are compared with normal values, *a*. A definite shortening of systole without any alteration in the length of diastole is seen. As shown in experiment 219, vii, *a* and *c*, a similar reduction of systole followed aortic compression even though diastole lengthened somewhat. Experiment 221, iii, shows normal data. After compression of the lower thoracic aorta as shown by data, v, systole decreased in length, diastole remained unchanged. When the aorta was stenosed in its ascending portion, however, as shown in vi, systole, on the contrary, lengthened, while diastole shortened. The data of experiment 231, vii, (table 2) are especially interesting, inasmuch as we have already considered the effects of increased

TABLE 2

The influence of increased arterial resistance on the duration of consecutive phases of the cardiac cycle

EXPERIMENT NO.	SYSTOLIC PHASES				DIASTOLIC PHASES					DIASTOLIC ARTERIAL PRESSURE	INITIAL PRESSURE (MM. Hg)
	Isometric contraction	Maximum ejection	Reduced ejection	Total systole	Proto-diastole	Isometric relaxation	Rapid inflow	Diastasis	Total diastole		
219, II											
a	0.040–0.052	0.065–0.085	0.052–0.068	0.167–0.180	0.015–0.020	0.060–0.085	0.050		0.200–0.230	35	8.0
*b	0.043	0.070	0.032–0.040	0.145–0.153	0.020	0.072–0.088	0.046		0.208–0.229	58	8.5
VII											
a	0.036–0.040	0.060–0.070	0.070	0.170–0.176	0.015–0.020	0.062–0.070	0.050–0.055		0.197–0.215	48	7.0
†c	0.040	0.055	0.065–0.070	0.160–0.165	0.011–0.020	0.091–0.098	0.062		0.223–0.242	63	12.0
221, III	0.058–0.06	0.110–0.115	0.085–0.090	0.258–0.260	0.020–0.022	0.085–0.089	0.060–0.065	0.025–0.030	0.275–0.292	52	7.4
†V	0.032–0.041	0.085–0 090	0.050–0.055	0.172–0.180	0.010–0.014	0.145–0.152	0.06	0.040–0.045	0.282–0.292	79	8.0
††VI	0.032–0.035	0.145–0.150	0.095–0.102	0.275–0.287					0.200–0.215	89	14.8
231, VII											
a	0.052–0.060	0.078–0.080	0.065–0.074	0.202–0.206	0.018–0.020	0.062–0.07	0.064–0.070		0.232–0.240	98	4.8
†b	0.050–0.055	0.067–0.072	0.062–0.070	0.184–0.190	0.013–0.014	0.076	0.055–0.060		0.232–0.234	108	5.3
‡†c	0.056–0.054	0.076–0.078	0.102	0.228–0.234	0.020–0.026	0.075–0.075	0.080–0.095	0.204	0.595–0.625	100	9.7
†d	0.042–0.045	0.100–0.110	0.050–0.055	0.195–0.200	0.016–0.025	0.068–0.073	0.100– (?)		0.246–0.265	138	5.6
XI	0.045–0.046	0.070–0.080	0.068–0.070	0.186–0.193	0.030–0.032	0.065–0.070	?	?	0.245–0.252	44	6.2
††XII	0.065–0.070	0.085–0.098	0.040–0.050	0.200–0.218	0.015–0.020	0.080–0.090	?	?	0.200–0.205	82	11.8
XVIII											
a	0.04	0.070–0.080	0.105–0.110	0.220–0.225	0 025–0.037				0.265–0.295	36	6.0
††b	0.035–0.04	0.150–0.175	0.040–0.045	0.235–0.245	0 020–0.03				0 260–0.275	79	14.2
234, I	0.050–0.060	0.100–0.110	0.09 –0.105	0.253–0.260	0 020–0.022	0.048–0.058	0.055–0.070	0.185–0.255	0.452–0.496	90	9.3
†V											
c	0.049–0.060	0.143–0.178	0.00 –0.040	0.227–0.243	0.020–0.022	0.070–0.080	0.060–0.088	0.232–0.244	0.484–0.548	104	9.7
†d	0.064–0.068	0.126–0.15	0.038–0.04	0.234–0.252	0.022–0.025	0.074–0.083	0.083–0.102	0.335–0.427	0.659–0.735	109	9.9

* Increased vasoconstriction.

† Aortic compression.

†† Aortic stenosis.

‡ Vagus stimulation.

venous inflow in this same experiment (table 1), *a* represents data of normal conditions in the closed chest; *b*, data obtained during compression of the abdominal aorta; a reduction of systole occurred without a change in the duration of diastole; *c* represents results obtained while the peripheral end of the right vagus was stimulated during compression of the aorta; systole lengthened with diastole; *d* shows effects shortly after cessation of stimulation while aortic compression was still retained, increased resistance clearly reduced the periods of systole. The chest was opened and the study continued; xi shows results of control data under these conditions; xii shows a lengthening of systole during moderate aortic stenosis. Similar lengthening is shown by comparing xviii, *b*, with the normal, *a*. In experiment 234 i represents data under normal conditions; v, *c*, the effect of compressing the abdominal aorta, and v, *d*, the effect of additional slowing. Systole was reduced as compared with normal even though diastole lengthened appreciably. *These data clearly show that increased resistance produced near the semilunar valves uniformly lengthens systole, while if the resistance change occurs more peripherally it tends to abbreviate systole.*

How may these contrary effects be explained? A clue was given by the observations that systole lengthens whenever the initial pressure is greatly elevated but that it shortens whenever initial pressure increases but little. In other words, the fact seems to stand out that *whenever initial pressure in the left ventricle increases considerably, whether as a result of increased resistance to ejection or from increased venous inflow, systole always lengthens.* Increased resistance without a material elevation of initial pressure has the contrary effect of abbreviating systole.

These reactions are in accord with those of skeletal muscles: If the initial tension of an after-loaded skeletal muscle is kept constant, while the lifted load is somewhat increased, the duration of the contraction phase is reduced, for the contractile stress is apparently overpowered sooner by a heavy than by a light load. If, however, the initial tension and initial length are increased at the same time that the lifted load becomes greater, then the contraction phase may lengthen. Returning to these experiments, it is evident that the chief variable introduced in the different experimental methods used to augment resistance consists in the length of elastic arteries interposed between the heart and the area where the resistance was actually increased. When the arterioles contract, diastolic pressure may be markedly elevated but a considerable stretch of elastic artery is still available to accommodate

any blood that may be ejected during systole. Consequently systolic retention is small, diastolic volume not greatly increased and the initial tension in the left ventricle rises but little. In such cases the greater arterial load acts to abbreviate systole. When the abdominal aorta is compressed, the accommodative power of the larger arteries is reduced, and the increase in diastolic volume and initial tension are not enough to overbalance the tendency of increased resistance to shorten systolic ejection. During aortic stenosis, however, the stretch of elastic aorta capable of accommodating ejected blood practically vanishes, consequently a large volume of blood must be retained within the ventricles at the end of each systole. This elevates the initial tension sufficiently to lenthen systole.

Such effects were also obtained by de Heer after production of aortic stenosis and appear to be the only conditions reproduced in the heart-lung preparation by Patterson, Piper and Starling. It is quite conceivable why this was the case. In such a preparation a rubber tube of comparatively small diameter was substituted for the aorta and its branches and all the ejected fluid was required to pass through a narrow cannula tied into the innominate artery. Under such artificial conditions the accommodative capacity of the system reaches its limits readily even when the arterial resistance is increased more peripherally.

Influence on systolic phases. Turning to the effects on the detailed phases of systole, we note no regularity in the changes of the isometric contraction phase. As a rule, the length of this phase varies little when resistance increases due to peripheral constriction or aortic compression, but if anything, a slight tendency to decrease is noted (e.g., exper. 219, ii, *b*, 221, v). During aortic stenosis, on the other hand, the phase generally lengthens somewhat (exper. 231, xii). Exceptions or, better stated, opposite effects occur, however, in many experiments (e.g., exper. 219, vii, 221, vi). The failure of this phase to lengthen consistently in all experiments emphasizes the relatively small importance which aortic pressure plays in determining the length of this phase. The actual shortening is undoubtedly explained as an effect of increased initial tension.

When systole shortens as a result of increased resistance of peripheral origin, the reduction occurs chiefly in the ejection phases. As a rule, the phase of reduced ejection is affected most and in extreme cases may practically disappear (exper. 219, ii). When, during aortic stenosis, systole lengthens, the maximum ejection phase is always prolonged

while the phase of reduced ejection is generally abridged (exper. 231, xii). Occasionally however it too may lengthen (e.g., exper. 221, vi).

Influence on phases of diastole. It may be anticipated that the great pressure existing at the very end of systole may act to close the semilunar valves more rapidly, i.e., decrease the proto-diastolic interval. Such a reduction was found in about 50 per cent of my experiments, being illustrated in table 2, by comparing the data of experiment 221, iii with v; experiment 231, vii, *a* with vii, *b* and experiment 231, xi with xii. The abbreviation, as might have been expected, is the more evident the nearer the aortic valves the resistance change takes place. The duration of the isometric relaxation phase was practically unaltered when increased resistance was occasioned by peripheral constriction (e.g., exper. 219, ii, *a*, *b*). In some experiments in which the abdominal aorta was compressed (e.g., exper. 221, iii, v) and in all cases were aortic stenosis supervened, (e.g., exper. 231, xi, xii) the phase lengthened definitely. While it is difficult to give a logical explanation of these changes, four factors, acting separately or together, may be thought of as effecting an increase in the length of an isometric relaxation phase, viz.:

1. The inherent rate of muscular relaxation during the isometric phase may be slower.

2. Intraventricular pressure being higher at the beginning of this phase, it might at the same rate of relaxation take more time for the pressure to decrease to the level of auricular pressure.

3. Since the opening of the a-v valves is determined by the balance of pressure in the auricle and ventricle toward the end of this phase, it is possible that either an increased intraventricular or a reduced auricular pressure might delay the opening of the a-v valves and hence prolong the isometric relaxation phase.

4. Finally, it is possible that the time interval by which the preceding protodiastolic phase is abridged is added to the phase of isometric relaxation.

After the a-v valves have opened, the continuation of the early diastolic inflow phase depends solely on the length of time during which a pressure difference between auricle and ventricle is maintained. A diastolic retention of blood and an increased intraventricular pressure certainly occur in cases of pronounced aortic stenosis. Consequently, it may be anticipated that the elevation of intraventricular pressure would much sooner retard the inflow and act to reduce the duration of this phase in this case. In none of the experiments in which the heart

was slow enough for a phase of diastasis to exist, was there, however, any evidence that the inflow phase is abridged during augmented arterial resistance of any kind. On the contrary there is, as shown in experiment 231, vii, *c*, at times a slight tendency for this phase to lengthen.

THE INFLUENCE OF HEART RATE

Influence on duration of systole and diastole. Section of both vagi nerves producing a tachycardia by giving the tonically active accelerators unopposed control, uniformly decreases the duration of systole even when, as happened a few times, the length of diastole is unaffected. The injection of small doses of epinephrin causes a further decrease in the length of systole which persists even when the vagi are stimulated in addition, and the heart in consequence becomes very slow.

The details of an experiment substantiating these deductions are summarized in table 3, experiment 231.

The changes that take place when the heart is slowed depend on the method through which the inhibitory influence of the vagus is brought into action. When the peripheral end of a vagus nerve is stimulated electrically, the systole: diastole ratios conform to a standard curve only when new and constant dynamic relations have been reëstablished (e.g., exper. 228, viii). During the time that the systemic pressures decline, changes in systolic length are in no sense related to the length of previous diastole. There is constantly a progressive increase in the duration of systole as stimulation continues and this occurs quite regardless of previous diastole. When stimulation has ceased, the diastoles are promptly shortened but systoles only gradually and progressively regain their former lengths. These observations, illustrated by the plots of experiments 216 and 232 in figure 1, are but confirmatory of independent observations recently published by Katz (3). Such results really need no additional comment, yet attention may be drawn to a striking relation shown in experiment 216. The heart beat at the end of stimulation had a diastolic length of 0.237 second with a systolic period of 0.195 second—this period being precisely equivalent to a systolic interval accompanying an earlier vagal beat having a diastole length of 1.819 second. A similar lack of relation was obtained when the heart was reflexly slowed by stimulation of the central end of one vagus nerve. The significant observation may be added that it often happened that, when conditions had been stabilized, systole was more prolonged by reflex than by direct vagal slowing although

TABLE 3

The effects of stabilized changes in heart-rate on the duration of the consecutive phases of the cardiac cycle

EXPERIMENT NO.	NATURE OF EXPERIMENT	PHASES OF SYSTOLE				PHASES OF DIASTOLE					ARTERIAL PRESSURE	EFFECTIVE VENOUS PRESS. (MM Hg)
		Isometric contraction	Maximum ejection	Reduced ejection	Total systole	Proto-diastole	Isometric relaxation	Rapid inflow	Diastasis	Total diastole		
228												
I	Control	0.044–0.048	0.080–0.082	0.075–0.080	0.200–0.207	0.021–0.023	0.065–0.078	0.065–0.078	0.04 –0.065	0.291–0.408	74	6.1
IV	Epinephrin	0.020–0.030	0.070–0.085	0.055–0.072	0.159–0.180	0.015–0.022				0.475–1.287	118	7.8
V	Left vagus cut	0.042–0.045	0.075–0.092	0.040–0.060	0.174–0.180	0.015–0.024				0.289–0.299	77	5.8
VI	Central vagus stimulated	0.056–0.055	0.118–0.135	0.082–0.090	0.263–0.267	0.025–0.027				0.657–0.665	98	8.2
VIII	Peripheral vagus stimlated	0.048–0.05	0.110–0.118	0.088–0.098	0.236–0.252	0.024–0.028				0.669–1.198	46	7.4
IX	Normal control	0.045–0.050	0.098–0.102	0.030–0.040	0.177–0.186	0.016–0.020				0.230–0.240	78	6.0
231												
I	Control	0.052–0.058	0.080–0.096	0.058–0.078	0.199–0.216	0.015–0.022	0.040–0.052	0.044–0.055	0.000–0.055	0.250–0.260	94	6.8
II	Right vagus cut	0.048–0.052	0.080–0.086	0.054–0.060	0.183–0.192	0.016–0.025	0.047–0.052	0.044–0.064		0.222–0.234	102	6.4
V	Left vagus cut	0.052–0.058	0.072–0.082	0.064–0.070	0.194–0.210	0.015–0.024	0.042–0.064	0.060–0.068	0.02 –0.03	0.245–0.259	102	6.4

IX													
a	Control later	0.044–0.045	0.078–0.080	0.062–0.068	0.187–0.190	0.018–0.020	0.053–0.056	0.062–0.063		0.235–0.239	100	6.0
b	Epinephrin	0.041–0.045	0.052–0.058	0.038–0.048	0.135–0.143	0.015–p.02	0.052–0.055	0.05		0.185–0.203	132	6.5
c	Peripheral vagus stimulated during epinephrin	0.038–0.045	0.055–0.070	0.038–0.070	0.133–0.182	0.024–0.038	0.045–0.072	0.06 –0.08	0.260–0.330	0.530–0.757	100	7.8
225												
II b	Asphyxia	0.038–0.040	0.098–0.106	0.064–0.095	0.208–0.213	0.018–0.027	0.068–0.073	0.124–0.125	0.160–0.349	0.413–0.702	74	11.3
IV b	Control	0.046–0.056	0.051–0.060	0.072–0.084	0.182–0.186	0.03 –0.033	0.058–0.063	0.080–0.081	0.000	0.218–0.225	51	4.3
219												
a	Control	0.040–0.042	0.073–0.080	0.032–0.038	0.153	0.015	0.063–0.070			0.195	38	7.8
b	Early stage asphyxia	0.040–0.041	0.062–0.065	0.031–0.045	0.147–0.148	0.010–0.014	0.060–0.072			0.184–0.208	59	9.7
c	Later stage	0.035–0.042	0.070	0.022–0.025	0.127–0.134	0.010–0.015	0.058–0.062			0.422–0.485	73	12.8

diastole was always much larger in the latter case (cf. exper. 228, vi and viii, table 3). The effect of vagal slowing by partial asphyxiation was determined in 14 experiments. In 4 cases only was there a lengthening of systole during beats with long diastoles which are at all comparable to direct or reflex vagal stimulation. In two experiments, systole lengthened very little; in two others, no change of systole was apparent although diastole lengthened markedly. Of even greater interest are six other experiments in which systole consistently *decreased* in length while diastole increased. Thus in one of these experiments, the systole : diastole ratio was $\frac{0.175}{0.187}$ before slowing, $\frac{0.149}{0.42}$ and $\frac{0.142}{0.70}$ at different times during slowing process. The changes

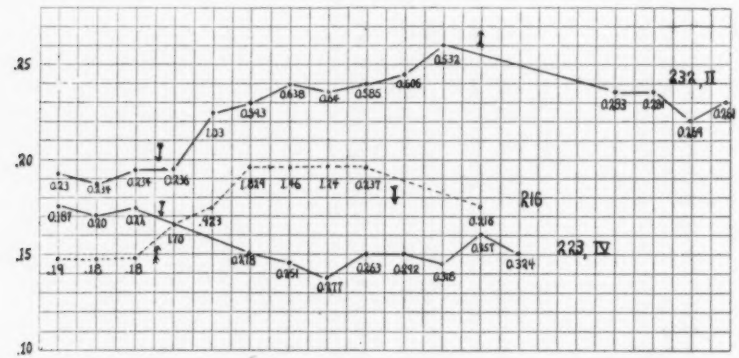

Fig. 1. Plots showing the lack of relation between durations of systoles and preceding diastoles. Experiments 216 and 232, ii, show changes during electrical vagus stimulation; experiment 233, iv, shows shortening effect of asphyxial slowing. Dots on ordinates indicate durations of successive systoles; figures beneath indicate lengths of preceding diastoles.

in consecutive beats of another experiment where only a moderate slowing occurred are shown as plot of experiment 223, in figure 1. Similar reactions take place after the administration of epinephrin. If the vagi are intact and the heart slows, the lengthening of diastole is accompanied by a decrease in the duration of systole (e.g., exper. 228, iv, table 3). If the vagi are divided and one of the vagus nerves is then stimulated while epinephrin is acting, the phase of systole remains diminished while diastole increases in length (e.g., exper. 231, ix, *a*, *b*, *c*, table 3).

It is quite apparent from such observations that the variations of systole when vagal slowing is accompanied by marked dynamic changes do not correspond with those obtained when the vagus is stimulated directly. This is probably accounted for by the fact that still other factors (e.g., simultaneous stimulation of the accelerator nerves, mechanical influence of high blood pressure or altered venous return) affect the duration of systole in an opposite direction. The balance of such opposing forces determines whether systole actually lengthens, shortens or remains unaltered as the cycles change. The detailed factors at work will be analyzed more at length in a subsequent portion of this paper. It may be profitable, however, at once to direct attention to the fact that high arterial pressure is one influence capable of counteracting the lengthening influence exerted by vagus slowing. Thus, in experiment 234, i, *v*, *c* (table 2) in which both vagi nerves were left intact, compression of the abdominal aorta first decreased the duration of systole without affecting the diastolic length appreciably. When later (*v*, *d*) a natural reflex slowing was initiated by the high arterial pressure, systole lengthened again but not above the duration it had at much more rapid rates.

Effects on systolic phases. As long as marked variations in systemic resistance or initial tension do not occur, the duration of the isometric phase is not permanently altered. This is true, e.g., during cardiac acceleration following vagotomy (e.g., exper. 231, i, v). Similarly there is no permanent change when the peripheral end of the vagus is stimulated (e.g., exper. 231, ix, *c*, 228, viii). When cardiac slowing is accompanied by drastic elevation in arterial resistance and initial tension, e.g., during asphyxia (exper. 225, ii, *b*) or during the action of epinephrin in animals with vagi intact (exper. 228, iv, table 3), then the isometric phase is definitely and permanently reduced. When, on the other hand, epinephrin simultaneously causes a great elevation of arterial pressure and cardiac acceleration in animals with vagi cut, this phase is not affected (exper. 231, ix, *a* and *b*, table 3). This would indicate that the reduction in the isometric phase is attributable neither to a specific effect of epinephrin on the accelerator mechanisms or on the heart itself nor to the height of arterial tension, but rather to the initial tension which determined the rate of pressure development. When epinephrin causes cardiac slowing, initial tension is markedly increased (exper. 228, iv). In cases where it causes acceleration, it is not greatly affected (exper. 231, ix, *b*). That this is indeed a factor is shown in experiment 231, ix, *c* where, upon additional stimulation of

the vagus nerve, the phase is promptly abridged when the initial tension is increased.

Since the isometric contraction phase alters only in exceptional cases, i.e., where the initial tension is greatly increased, and in these, in fact, tends to shorten, it is obvious that alterations in the duration of systole are almost entirely due to changes in the ejection phase. It will be recalled that whenever the heart is slowed through direct or reflex vagus stimulation, the interval of systole progressively increases, and that this is related neither to the duration of previous diastole nor to the diastolic arterial pressure. On the other hand epinephrin,

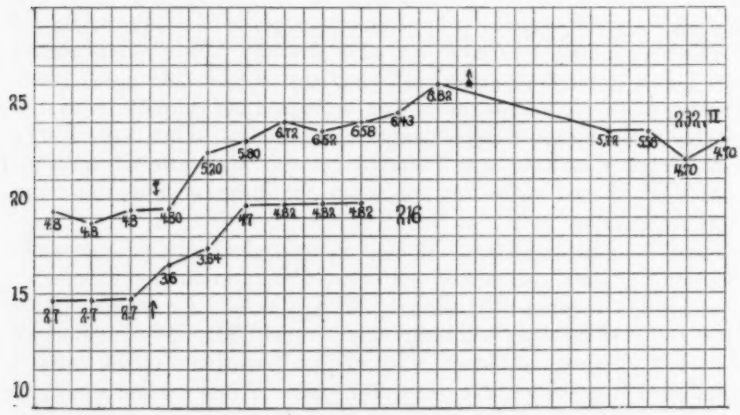

Fig. 2. Plots showing the relation between initial intraventricular pressure and duration of systoles, during vagus slowing. Same experiments and plot as in figure 1, except that figures beneath dots indicate the initial intraventricular pressures in mm. of Hg.

asphyxia or slowing fail to increase this interval. These variations in systolic lengths are paralleled by changes in the length of the ejection phases.

The progressive lengthening of the systolic ejection phases is accompanied by a progressive increase in the initial pressure and in fact no further lengthening occurs when the initial pressure also fails to increase further (fig. 2). Since an increase in initial tension lengthens the ejection phase it is probable that it is the factor which influences the duration of this phase in cases where the heart rate changes. This explains why systolic ejection remains lengthened for a considerable number of beats after the return of the heart to a more rapid rate.

The conclusion may be drawn that when the heart changes its rate, the duration of systolic ejection and hence that of systole is determined not only by the previous diastole length, but often, to a far greater extent, by the variation in initial tension within the ventricle.

It remains to interpret the cases where the systolic ejection was reduced or unaltered, for both during asphyxia and during the action of epinephrin the initial tension is also increased. One and possibly two other factors then counteract such an effect of augmented initial tension to lengthen the period of systolic ejection and consequently also that of systole. It has already been pointed out that a great increase in arterial resistance tends to reduce the ejection phase and, as this operates intensely during asphyxia and epinephrin action, we have two counteracting tendencies at work—the augmented initial pressure tendency to lengthen and the increased arterial resistance acting to abbreviate this phase. The relative influence of these factors determines whether systolic ejection is slightly lengthened, unaltered or, as frequently happens, actually abbreviated.

In the case of slowing induced by epinephrin, at least another factor can not be ruled out, viz., a specific effect on the accelerator mechanisms. That this is concerned is indicated by such observations as are recorded in experiment 231, ix, table 3. In this case a small dose of such a solution caused an increase in the cardiac rate, an elevation of diastolic arterial pressure and a pronounced decrease in the systolic ejection phase. During additional vagus stimulation (ix, *c*) when the arterial pressure returned to normal and in spite of an elevation of initial pressure and a prolonged diastole, systole was still less than normal.

Effects on diastolic phases. Changes in heart rate produce only very minor changes in the duration of the diastolic phases. As before indicated, the duration of the proto-diastolic phase is so short that no pronounced changes may be anticipated. This was the case except in a few experiments in which the duration slightly decreased after direct or reflex vagus stimulation (exper. 228, vi, viii). The duration of the isometric relaxation phase was not affected during slowing beyond the range of error with the exception of two cases (e.g., exper. 231, ix, *c*) in which an increase of about 0.2 second occurred in some beats. Similarly, a slight increase was obtained in three asphyxial experiments. It is apparent that, with few exceptions, which, as a matter of fact, do not show any extreme change in the isometric phase of relaxation, it remains unaltered during various types of vagal slowing. No evidence

has been found that the early diastolic inflow phase increases in length during cardiac slowing of any type (table 3). These observations give probability to the view that, as regards time relations at least, the diastolic inflow period is entirely superimposable during vagus slowing.

SUMMARY AND CONCLUSIONS

Since previous observations had indicated that the duration of systole is not entirely determined by the length of previous diastole, an investigation was undertaken to determine what other factors might be concerned. The following conclusions were reached:

1. An increase in venous return above normal causes a lengthening of ventricular systole, quite independent of diastole length. This occurs as a result of the prolongation of the ejection phases, the isometric phase of contraction having a tendency to be abridged. Since the initial pressure was always elevated when this occurred, we may formulate the conception that, whether or not the mechanical energy liberated by contraction is fundamentally determined by the initial length of the ventricular fibers at the inception of contraction, the duration of systole, at constant heart rates, varies directly as the initial intraventricular pressure under such a variety of inflow conditions as it is possible to produce in the mammalian heart in situ.

2. An increase in arterial resistance acts to abbreviate systole, independently of changes in diastolic length. This abbreviation of systole takes place in spite of a slight tendency of the isometric phase to lengthen and is therefore due to a shortening of the ejection phase. This shortening of the contraction phase is apparently due as in skeletal muscle, to the fact that the muscular shortening is terminated earlier by the greater load acting during the process of shortening.

3. When the increase in arterial resistance is of such grade and type that the ventricle can not empty itself effectively, a marked retention of blood occurs, and the diastolic volume and initial tension increase, in consequence. As such an increase in initial pressure has a tendency to lengthen systole, two opposing influences come into operation in such elevation of arterial resistance, viz., *a*, the tendency of higher arterial resistance to abbreviate; and *b*, the tendency of increased initial tension to lengthen systole. Both factors, no doubt, operate to influence the duration of systole whenever the arterial resistance is increased, but one factor usually predominates. When arterial resistance increases as a result of intense peripheral vasoconstriction, systolic retention is not pronounced and initial tension only slightly

increased. Consequently the first factor predominates, and systole decreases. When the aorta is stenosed, the accommodative capacity of the aorta is reduced and large volumes of blood are retained within the ventricle, consequently the initial tension increases very markedly. The second factor then predominates and systole lengthens. When the elasticity of the arterial system or the caliber of the vessels is insufficient to accommodate readily the systolic volume expelled by the ventricles, an increase in peripheral resistance may also act to elevate initial tension and lengthen systole. This explains the lengthening of systole consistently found by Patterson, Piper and Starling in the heart-lung preparation and we may expect to find such lengthening also in arteriosclerosis involving the larger vessels.

4. The duration of systole is determined solely by changes in the length of previous diastole *only* when the initial intraventricular pressures and the aortic pressure at the beginning of diastole remain nearly constant. Thus we find that, during vagal slowing and during the acceleration subsequent to such stimulation, the duration of systole is predominantly determined by changes in initial pressure, rather than the length of preceding diastole. Again, when slowing occurs in association with an elevation of arterial resistance as during asphyxia or epinephrin, the duration of systole may be abbreviated through the influence of such higher resistance. There is evidence also that in the case of adrenalin action or stimulation of the accelerator nerves, there is a specific effect on the ventricle which acts independent of these influences to shorten the contraction phase.

5. These observations indicate that not only under abnormal conditions of venous and arterial pressures but also under such conditions as may be considered quite normal, the *systolic portion* of the ventricular volume curves can not be regarded as superimposable at different rates of beat.

6. Since the phases of diastole alter so little in duration, however, during the most diverse conditions of the circulation, it is not possible from these observations to draw the same deductions in regard to the superimposability of diastolic portions of the volume curves.

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THE EFFECT OF SHORT SPELLS OF REST ON PHYSICAL EFFICIENCY AS MEASURED BY A BICYCLE ERGOMETER[1]

LUCY A. WALLRICH AND PERCY M. DAWSON

From the Physiological Laboratory of the University of Wisconsin

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Introduction. It has been stated (1) that when physical labor is in character very severe, an increase in efficiency can be brought about by interrupting the work at rather short intervals with spells of rest. For example, in trench digging the interruption of work every 5 minutes by a period of 10 minutes' rest was found more productive than when the work was performed continuously. Again in the heavy work of moulding in a large munition factory, it was found advantageous from the point of view of production to rest 15 minutes once in every hour.

Wishing to observe a little more minutely the relation of the severity of the exertion to the effect of spells of rest upon production, the following investigation was undertaken.

Method. The method employed was to determine the number of revolutions of the wheel of a bicycle ergometer. Upon this wheel rested a brake which could be weighted to a known degree. Two subjects were used: M. M. J., female, 22 years, physical education student; and P. M. D., male, 46 years, university professor. Each of these subjects performed two series of experiments. The first consisted in riding *continuously* for one hour; the second, in *interrupting* the rides in such a manner that every 10 minutes of riding was followed by a 5-minute period of rest.

Results. The results of these experiments are shown in tables 1 and 2 and figures 1 and 2, which are sufficiently explained in their legends and require only a brief comment in this place.

[1] The material used in writing this article was first collected in the B. A. Thesis of Lucy A. Wallrich submitted to the University of Wisconsin in 1919. It was also reported briefly before the American Physiological Society (this Journal, 1921, lv, 314).

On perusing the tables and figures it is interesting to observe how there is gradually approached and finally passed over a neutral point, a point where it is quite indifferent whether the ride is interrupted by spells of rest or is not. The subject is quite unconscious of this neutral

TABLE 1

KILOS	INTERMITTENT		CONTINUOUS	
	Date	Revolutions	Revolutions	Date
8	January 13	7,810	13,423	January 29
8	January 25	9,391	12,534	February 5
8	February 1	10,312	8,313	February 15
8	February 8	10,160		
8	February 19	9,074		
	Average	9,349	11,423	Average
16	March 7	3,946	2,050	February 27
16	March 25	4,918	3,668	March 22
16	March 28	4,533	3,823	March 31
16	April 2	4,752	3,943	April 4
16	April 5	4,000	4,078	April 6
16	April 11	5,176	6,895	April 9
16	April 21	5,204	6,405	April 14
16	April 26	4,636	6,539	April 18
	Average	4,652	4,550	Average
12	April 28	6,370	7,740	May 6

Table 1. Shows the results of the two series of rides performed by the subject P. M. D. Note *a*, with 8 kilo brake the number of revolutions is usually higher (average much higher) when the ride is continuous; *b*, with 12 kilos only two rides were performed; of these the continuous ride showed a greater number of revolutions; *c*, with 16 kilo brake the number of revolutions was at first much less when the ride was continuous and then much greater. The averages in this case are not significant as it is certain that the relation would have been reversed had the number of rides been increased.

point and of his relation to it. Doubtless the passage over this point in the reverse direction occurs during relatively slight indispositions. The necessity of fitting the task not only to the particular operative or athlete but to the particular physical condition in which the individual finds himself is obvious.

TABLE 2

KILOS	INTERMITTENT		CONTINUOUS	
	Date	Revolutions	Revolutions	Date
4	January 18	4,933		
4	January 22	5,105		
4	January 24	5,659		
4	January 25	5,577		
4	January 29	5,906		
4	January 31	6,091		
4	February 1	6,412		
4	February 6	5,294		
4	February 7	5,438		
4	February 19	6,783	10,233	February 20
4	February 26	5,910	10,745	February 24
	Average	5,737	10,489	Average
8	March 7	5,790		
8	March 8	5,402		
8	April 1	5,896	7,361	April 2
8	April 3	5,945	6,620	April 4
	Average	5,758	6,990	Average
12	April 8	4,039	4,890	April 17
12	April 19	4,444	5,152	May 13
12	May 7	4,359	5,948	May 10
	Average	4,281	5,330	Average

Table 2. Shows the results of the two series of rides performed by the subject M. M. J. Note *a*, with 4 kilo brake the number is always much higher when the ride is continuous; *b*, with 8 kilos the same is true but the difference between the results of the continuous and those of the intermittent rides is less; *c*, with 12 kilos the difference is still less although it remains in favor of the continuous rides. Without doubt the addition of a couple more kilos would—as in the other subject (P. M. D.)—have transferred the advantage to the intermittent ride.

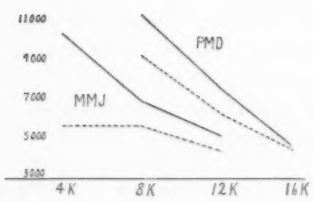

Fig. 1

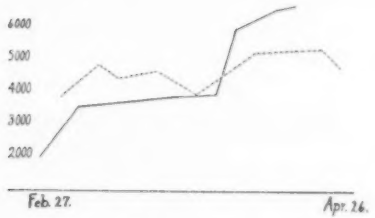

Fig. 2

Fig. 1. Effect of increasing the weight upon the number of revolutions per hour. Ordinates represent number of revolutions of cycle ergometer; abscissae, weight on brake; solid lines, continuous riding; broken lines, interrupted riding. Each point on the curves represents the average of several rides. *Note that as the weight upon the brake was increased the advantage of the continuous over the interrupted work was decreased.*

Fig. 2. Effect of practice and improved physical condition upon the number of revolutions per hour with a heavy brake; 16 kilos. Ordinates represent number of revolutions of cycle ergometer; abscissae sequence of rides from February 27 to April 26; solid lines, continuous riding; broken lines, interrupted riding. Each point on the curves represents a single ride. *Note that as the subject became practiced and his physical condition improved, the advantage of the spells of rest decreased, disappeared and was finally transformed into disadvantage.*

CONCLUSIONS

1. When exercise is *heavy*, efficiency is increased by spells of rest.
2. When exercise is *light*, efficiency is decreased by spells of rest.
3. The neutral point, viz., where work is neither light nor heavy, varies with the individual.
4. The neutral point varies in the same individual depending on practice and physical condition (training).

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THE SURFACE TEMPERATURE OF THE ELEPHANT, RHINOCEROS AND HIPPOPOTAMUS

FRANCIS G. BENEDICT, EDWARD L. FOX AND MARION L. BAKER

From the Nutrition Laboratory of the Carnegie Institution of Washington, Boston, Mass., and the New York Zoölogical Park, New York City

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The importance in the animal economy of the loss of heat by radiation, conduction and vaporization of water, justifies a study of the factors governing this loss. Among these factors of no small significance is the surface, i.e., skin temperature, particularly as influenced by the nature of the integument and by the presence or absence of protective covering, such as hair, fur, feathers or, in the case of civilized man, clothing. Observations of the skin temperature of both clothed and nude humans have been in progress in the Nutrition Laboratory for a number of years. With many of the domestic animals numerous data for the skin temperature are recorded in the literature, but these were for the most part taken outside of the fur covering or the attempt was made to secure the observations at the skin well covered with fur. It is obvious that skin temperature measurements obtained under these conditions are not only uncertain but likewise difficult of interpretation, because of the large mass of stagnant warm air contained in the fur. For comparison with the data obtained with nude humans, therefore, the most accurate and most immediate results are secured only with those lower animals that are hairless.

In connection with a series of observations at the New York Zoölogical Park, which has coöperated with the Nutrition Laboratory for a number of years in the study of the metabolism of some of the lower animals, it became possible to obtain skin temperature measurements on several of the large pachyderms. The liberal scientific policy of Dr. W. T. Hornaday, the Director of the New York Zoölogical Park, and particularly the friendly coöperation of Mr. Raymond L. Ditmars, the Assistant Curator of Mammals and Curator of Reptiles, enabled us to make an intensive study of the skin temperature of two elephants, one rhinoceros and a hippopotamus. These animals are, for the most part,

well used to handling by man, and while obviously in captivity and therefore under artificial conditions, nevertheless have lived under these conditions for a decade or more and hence may be fairly said to have adjusted themselves to their present environment.

A thermo-electric method of taking skin temperature measurements has been carefully tested in the Nutrition Laboratory and a preliminary communication has already been made with regard to certain results obtained upon a human subject, both clothed and nude, after several hours of exposure to cold.[1] Since the animals chosen for the study reported in this second paper were in many instances very restless and only a few seconds could at times be taken to secure the temperature records, this thermo-electric method was ideally adapted for our purpose as it permits extremely rapid and accurate measurements. Fortunately, repeated tests of our apparatus have shown that a 6-second period of application of the thermo-junction suffices to give the true skin temperature.

The apparatus consists of two copper-constantan thermo-junctions, one of which is applied directly to the skin, while the other is placed in a thermos bottle carrying a tenth degree Centigrade thermometer, which can be read to hundredths. The terminal wires lead to a galvanometer which is of such a degree of sensitivity that each millimeter scale deflection corresponds approximately to 0.06°C. The galvanometer was of a fairly low resistance, long leads could easily be used, and this made it possible to go into the farther corners of the several animal compartments without having to carry in delicate electrical apparatus, with the danger of breakage. The constant temperature junction (held at about 30°C.) was read practically every 3 or 4 minutes, and approximately every hour the galvanometer "constant" was verified. In the operation of taking the temperature measurements one of us was at the galvanometer to read and make records of the deflections on the scale, one applied the junction to the skin, and the third determined with a pen point on a series of sketches, outline drawings or picture postcards, the exact location of the measurement, this location being given a number for subsequent reference. With a piece of chalk each point of application was marked on the animal's hide, and subsequent readings could be taken at the same point for a check and control.

The skin temperature of a female Indian elephant and a male African elephant. The first animal studied was a female Indian elephant, *Elephas indicus* (*Cuv.*). At the time of our measurements she was

[1] Benedict, Miles and Johnson: Proc. Nat. Acad. Sci., 1919, v, 218.

25 years old, her estimated weight was 6300 pounds, and she was 8 feet $5\frac{1}{2}$ inches tall, 10 feet $7\frac{3}{4}$ inches long, and 4 feet 1 inch broad. This animal, while thoroughly tractable and frequently used in summer to carry children about the Park, was very nervous. The application of the thermo-junction seemed to startle her and it required some training to secure satisfactory readings. The incessant activity of the animal likewise made the measurements difficult. Indeed, it is probably correct to state that at no time during our entire experience, covering several days, was either elephant motionless for two consecutive seconds.

While the temperature of the elephant house was kept relatively constant at about 19.5°C., the weather at the time of our observations was extremely cold and not infrequently a perceptibly cold draft from one of the skylights and pronounced wind drafts from the wall could be felt about the elephant's body. We have reason to believe that these drafts at times materially affected the surface temperatures of the animals. Thus, for example, when the series of measurements was repeated on the second day, considerable differences in skin temperature amounting to 3° or 4°C. were noticed in the same spot. Owing to the inquisitiveness and restlessness of the elephant, it was impossible to place a psychrometer within reach of or anywhere near the animal. The psychrometer was, however, placed around the corner in an adjoining compartment, under practically the same atmospheric conditions, and the temperature of the wet bulb was found to be on the average 10.9°C. throughout our observations.

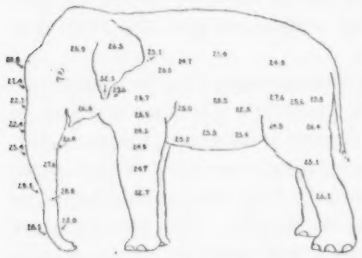

Fig. 1. Surface temperatures of a female Indian elephant (left side). Temperature of environment, 19.5°C.

A topographical survey of the skin temperature of this female Indian elephant is given in figure 1. In this and the following diagrams are given *only* measurements on the unprotected skin areas. Each record represents in most cases the average of a number of measurements, but occasionally a single measurement. The decimal point in each number serves to indicate the exact location of the measurement; in a few instances where this method could not be advantageously adhered to, an arrow points to the location of the measurement. Figure 1 represents the left side of the Indian elephant, since practically all

of the observations were made upon this side. A few temperature measurements were also obtained on the right side of the body, two points on the exterior surface of the ear giving 23.7°C. and 24.1°C., respectively, and two points on the right shoulder giving 26.2°C. and 25.0°C.

The relatively high values found around the lower end of the trunk, particularly on the inside of the trunk, may be explained by the fact that the expired air was constantly being blown against these parts. In the semi-enclosed places, such as the groin and axilla, high values were normally to be expected.

On the ear extraordinarily high temperatures were found. In general, the temperature on the inside of the ear was somewhat warmer than that on the outside, but one would normally expect that the tip end of the ear would be relatively cold, as is the case with humans. As a matter of fact, the warmest spot on this animal's entire surface was on the tip end of the left ear, where two records averaging 32.5°C. were obtained. Although it was impossible to make a very close examination of the ear and the skin was so rough that veins or arteries could not be seen, every effort was made to take a sufficient number of observations to be sure we were not dealing with the temperature taken directly over an artery. The two figures obtained at the tip end of the left ear of 31.6°C. and 33.4°C. may therefore be considered as certainly characteristic of the temperature at this particular point and at the particular moment. Indeed, the temperature at this point was so high that, when called to the attention of the keepers, it was noted by the hand alone.

The right ear of this elephant gave at no point temperatures as high as those found on the left ear, the highest record obtained at any time being 24.1°C. at a point approximately equivalent to where an average of 32.5°C. was found on the left ear. This difference of substantially 8° we are unable to explain. The keepers looked for a possible abscess as a result of the use of an elephant hook, but nothing could be found to account for the high temperature. With the other elephant a similar observation of high temperature on the tip of the ear was made. Furthermore, it should be stated that on the three days during which we studied the elephants, marked differences in the temperature of the two ears and, indeed, very wide and relatively rapid changes in temperature on the periphery of the ear were frequently noted, thus suggesting a large blood supply even to the tip of the ear.

In general, as seen from figure 1, there is a fairly uniform temperature distribution over the skin of this Indian elephant, the average skin temperature being close to 25.5°C.

Skin temperature measurements were likewise secured with a male African elephant, *Elephas oxytis* (*Matschie*), which at the time of our observations was 15 years old, 9 feet $3\frac{1}{4}$ inches tall, 11 feet $1\frac{1}{4}$ inches long, 3 feet 7 inches broad, and had an estimated weight of 6000 pounds. This animal, though not considered so peaceful and tractable as the female Indian elephant, having at times shown a rather unruly disposition, proved to be extraordinarily docile in the hands of his keeper, Mr. Walter Thuman, and, aside from the inevitable inquisitiveness and restlessness, permitted measurements ad libitum.

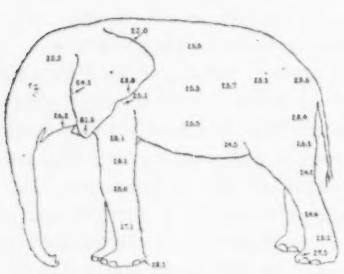

Fig. 2

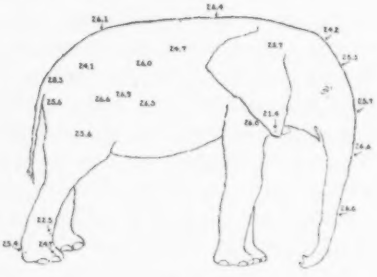

Fig. 3

Fig. 2. Surface temperatures of a male African elephant (left side). Temperature of environment, 19.5°C.

Fig. 3. Surface temperatures of a male African elephant (right side). Temperature of environment, 19.5°C.

Two somewhat extensive series of measurements were made upon him on consecutive days. Both the left and the right sides were studied, primarily with a view to noting if there was anything in the nature of a general unilateral temperature distribution, as suggested by the curious changes noted in the ear temperatures. The average values obtained on the left side of this elephant are charted in figure 2 and those on the right side in figure 3. While a careful study of the figures will show that there was not perfect equality in the temperatures at any two corresponding spots on opposite sides of the body, nevertheless if we take into consideration the differences in temperature of the same spot noted at different times of the day and on different days, there is nothing in the data to warrant even a suspicion of a unilateral temperature

distribution. Attention should be called again to the extraordinarily high values found at the tip of the left ear, where one would ordinarily expect low temperatures. The back of the ear, i.e., in a protected area, had on the whole a higher temperature than the front, and very marked differences were observed in relatively small areas. In this connection it should be noted that the ears of the African elephant are considerably larger than those of the Indian elephant.

The semi-enclosed parts, such as the groin and the axilla, and particularly around the ear and the inside of the trunk, were characterized by relatively high temperatures. The highest individual reading noted on this animal was 33.6°C. well up in the groin. On the soles of the feet temperatures were recorded of 24.3°C. on the left hind foot and 25.4°C. on the left front foot.

All the observations taken with this animal seem to indicate a considerably higher temperature down the front leg than down the hind legs. It should be pointed out that this conclusion is based upon only one series of temperature measurements down the front leg from the shoulders to the toes, and it is to be regretted that a second series was not obtained over this same area on the other front leg. As a matter of fact, the computations of the temperature measurements were not made until some time after the actual observations were recorded, and hence this point was not clearly brought out until later. Since this particular elephant was somewhat sensitive to being touched toward the outer end of the trunk, very few observations could be obtained there. The general picture of the data recorded for this male African elephant shows an average skin temperature essentially that observed with the female Indian elephant, i.e., 25.5°C.

The rectal temperature of elephants has not been extensively recorded. Dr. W. R. Blair of the New York Zoölogical Park has furnished us with the following information with regard to rectal temperatures taken by himself to establish normal values. With the Indian elephant he has found rectal temperatures of 97.4°F., 97.2°F. and 98°F. (i.e., 36.2° to 36.7°C.). Our own observations on the rectal temperature of the African elephant gave values of 35.90°C. and 35.85°C. Realizing that the relatively large masses of feces passed by these animals, falling upon a fairly warm concrete floor, would probably lose heat very slowly in the center, a thermometer was thrust into the warm, moist mass of feces as quickly as it was passed, and a record was thus obtained of 36.7°C. for the temperature of the feces of the female elephant and 36.2°C. for those of the male elephant. It is probably true, therefore,

that the rectal temperature of the elephant is not far from that of the human body, possibly slightly lower than the average usually accepted for man, which is 37°C.

The skin temperature of a black African rhinoceros. The rhinoceros in the New York Zoölogical Park, a female, although reputed to be rather intractable, was, as a matter of fact, a most willing subject. As a rule she remained standing very quietly, and on one occasion actually went to sleep, lying on her side, thus affording the best possible opportunity for obtaining the temperatures in the groin and on the soles of the feet. This animal, of the species known as *Rhinoceros bicornis* (*Linn.*), was born in 1905 and accordingly was 15 years old at the time of our measurements. Her estimated weight was 1900 pounds, and she was 4 feet 8 inches tall, 9 feet 6 inches long, and 2 feet 10 inches broad. Her skin, although extraordinarily thick, was much smoother than that of the elephants and thus gave much more satisfactory measurements.

In figure 4 are recorded only those temperatures found on the exposed surface of the skin on the left side of the body. Obviously in the groin and between the folds of skin high temperatures were noted, but these are not given in this diagram. There is a slight tendency for the lower temperatures to be found along the back rather than farther down the sides and belly. The highest temperature recorded on the skin was 27.9°C. on the left flank. Since the temperature of the environment in the rhinoceros compartment was essentially the same as that in the elephant compartment, it is clear that the rhinoceros had a slightly higher skin temperature than the elephant. In addition to the data given in figure 4 a number of records were obtained in the folds of the heavy skin. One record in a fold at the top of the head directly back of the ear showed 29.2°C. In the left axilla, deep in the fold, a temperature of 29.6°C. was found, while well up in the groin two records of 33.4°C. and 33.3°C. were obtained. Two records on the soles of the front feet gave 28.6°C. and 24.8°C., and on the sole of one of the hind feet a temperature of 26.5°C. was noted. The average skin temperature of this rhinoceros was 26.2°C., a value slightly higher than the average found with the elephants, which was 25.5°C.

We were able to secure one measurement of the rectal temperature of this rhinoceros, namely, 37.4°C. (99.3°F.), which compares very well with Doctor Blair's records for the Indian rhinoceros of 100°, 99.7° and 99.7°F.

The skin temperature of a male hippopotamus. A specimen of the *Hippopotamus amphibius* (*Linn.*), a male, was also studied. This animal was 18 years old, had an estimated weight of 4600 pounds, and was 4 feet 10 inches tall, 11 feet 6 inches long, and 4 feet 3 inches broad. He was accustomed to spend much of his time in the water in a large tank adjoining his compartment, the temperature of which was approximately 15°C., but several hours prior to the taking of the temperature measurements the tank was drained and the animal was kept in a dry space along with his food. At the time of our measure-

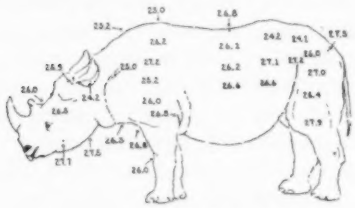

Fig. 4

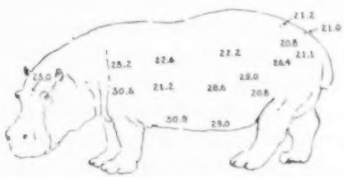

Fig. 5

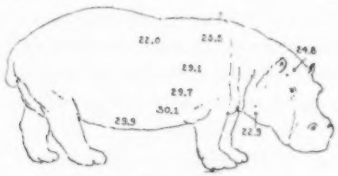

Fig. 6

Fig. 4. Surface temperatures of a female black African rhinoceros (left side). Temperature of environment, 19.5°C.

Fig. 5. Surface temperatures of a male hippopotamus (left side). Temperature of environment, 19.5°C.

Fig. 6. Surface temperatures of a male hippopotamus (right side). Temperature of environment, 19.5°C.

ments, therefore, the animal's body was reasonably dry, and while it felt slightly moist to the hand, no drops of water could be seen anywhere. The animal was extremely irritable and nervous, especially during the second series of observations; it was only with difficulty that we could secure the records here given, and we had to content ourselves with temperatures of the exposed skin, as it was impossible to measure the temperature in the groin, on the soles of the feet, or in any of the semi-enclosed cavities. The temperature topography of the hippopotamus is shown in figures 5 and 6 herewith, for the left and right sides, respectively.

From an inspection of the data in figures 5 and 6 it is clear that the skin temperatures are distinctly low as the back bone is approached, with a tendency for higher values down the side and under the belly. Even here the picture is not perfectly clear, since one extremely low value of 21.2°C. is noted near two high values of 30.6° and 30.9°C. The evidence is sufficient, however, to show that the lower half of the side of this animal has a relatively high temperature. It is not impossible that the lower temperatures on the upper part of the side are due to the vaporization of moisture from the skin and likewise to the possible downward drafts of cold air from the skylight and the ventilators in the chamber. These drafts of air were not sufficient, however, to affect the temperature of the wet and dry bulb thermometer, which remained essentially constant throughout the entire 3-day test.

From the relatively few measurements here recorded in figures 5 and 6 it is somewhat hazardous to estimate an average skin temperature for this animal. But if we follow the practice carried out with the elephants and rhinoceros and assume the legitimacy of averaging these results, we find the average for this animal is not far from 25.0°C. The hippopotamus, therefore, has an average skin temperature essentially that of the other three animals studied, although very much greater differences were observed between the temperatures of the back and belly than were found with either of the two elephants or the rhinoceros.

The irritability and viciousness of this particular animal finally resulted in the complete demolition of certain parts of our apparatus, which prevented further readings. No rectal temperatures could be secured with the animal, and the feces were not of sufficient volume and consistency to make it possible to secure the temperature of the feces immediately after their passage. It is probably true, however, that the rectal temperature of the hippopotamus is not far from that of the other large animals we studied, i.e., essentially that of man.

Suggestions for further study. All of the diagrams show that an attempt was made to measure the temperature at a spot corresponding approximately to the forehead of man, which always has a temperature much higher than other exposed parts of the body. With all of these animals relatively low rather than high forehead temperatures were recorded. This brings up the interesting question as to the influence upon the forehead temperature of the supply of blood to the brain, this factor undoubtedly being complicated by the extraordinarily thick skull and very thick skin of these pachyderms. Almost nothing

is known with regard to the blood supply and arterial distribution of blood in these large animals and the importance and significance of a thick skin as protection against heat loss, nor indeed is anything yet known with regard to their total metabolism and heat production per unit of weight or per unit of surface area. Measurements of this type involve very large and elaborate apparatus and partake of the nature of an engineering rather than a physiological problem. Aside from expense, however, no technical difficulties stand in the way of actual measurements of this type, although undoubtedly indirect calorimetric determinations of the carbon-dioxide production and oxygen consumption will have to be made rather than direct calorimetric measurements. But whatever the heat production, undoubtedly the extremely thick skin of these animals plays an important rôle in the protection against heat loss.

It is to be hoped that at some time a series of temperature measurements may be made with hairless animals of the types here studied, when the environmental temperature is measurably higher and lower than 19.5°C. The higher environmental temperatures could readily be obtained in certain seasons of the year, but the practicability of subjecting these tropical animals to a temperature much lower than 19.5°C. without danger is a matter of much uncertainty.

SUMMARY

Measurements were made of the skin temperatures of a group of large captive, hairless animals, namely, two elephants, a rhinoceros and a hippopotamus. For a number of years these animals had been subjected to the same routine of life in a well-ordered animal house at the New York Zoölogical Park and had become thoroughly acclimated to the conditions. For several weeks, if not months, prior to this investigation they had been living in an environmental temperature essentially constant, i.e., 19.5°C., and with no great changes in the degree of humidity.

With the two elephants the average temperature of the skin was 25.5°C. Local conditions of environmental temperature and drafts affected the skin temperature. Very pronounced temperature gradients were observed on various parts of the ears and extraordinary temperature differences were found at the tips of the right and left ears, both on the front and back of the ears and on different days. Of the three types of animals studied the elephants were by far the most restless and

much more active, for example, than the rhinoceros, who remained standing still or lying down practically the entire time, while the elephants were standing up and continually in motion. It is well known that with humans during severe muscular work there is an increase in skin temperature. On the basis of increased activity resulting in increased metabolism, one would, therefore, normally have expected to find a slightly higher skin temperature with the elephants than with the rhinoceros, but the actual records show exactly the opposite. With the rhinoceros the average skin temperature, 26.2°C., is somewhat higher than with the male elephant. In the semi-enclosed places, such as the groin and axilla and, especially with the rhinoceros, between the folds of skin, very much higher temperatures are observed, a value as high as 33.4°C. being found with the rhinoceros well up in the groin. The hippopotamus, by reason of its moist skin and amphibious nature, has a very widely varying skin temperature. Its skin is considerably colder on the back than on the belly. The temperament of this animal made it difficult to secure a sufficient number of measurements, but a rough average gives a value for the skin temperature of 25°C., which is not far from that found with the elephants.

All these animals, therefore, may be said in general to have essentially the same skin temperature, averaging about 25.5°C., or about 6°C. above the environmental temperature of 19.5°C. The rectal temperature is essentially that of man. The fact that all four animals show approximately the same average skin temperature is of special significance and leads to the interesting query as to what would be the skin temperature of a man who remained nude and in an environmental temperature of 19.5°C. for a considerable length of time.

STUDIES ON THE RESPONSES OF THE CIRCULATION TO LOW OXYGEN TENSION

V. Stages in the Loss of Function of the Rhythm Producing and the Conducting Tissue of the Human Heart During Anoxemia

CHARLES W. GREENE and N. C. GILBERT

From the Department of Physiology and Pharmacology, Laboratory of Physiology, University of Missouri and the Department of Medicine, Northwestern University School of Medicine

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That systemic asphyxiation is a factor in producing slowing of the heart rhythm and in decreasing conductivity has long been known,—Klug (1), Konow and Stenbeck (2) and numerous later investigators. Our present views as to the anatomical differentiations within the heart have resulted from a series of papers presenting the morphological and physiological facts of the conducting and nodal system,—Kent (3), His (4), Keith and Flack (5), DeWitt (6), Mall (7), Lhamon (8), Eyster and Meek (9) and many others. The facts of the functional control of the heart rhythm and sequence from dominant centers as understood at the present time have been developed especially by Erlanger (10), Keith and Flack (5), Adam (11), Flack (12), Lewis (13), Ganter and Zahn (14), Meek and Eyster (15) and Lewis (16). The influence of temperature, of asphyxia, of drugs, and especially of the extrinsic nerves on the sino-auricular and auriculo-ventricular rhythms and on conduction have been discussed in several of the preceding references and also by McWilliam (17), Lewis and Mathison (18), Mathison (19), Meek and Eyster (20), Eyster and Meek (21), Schlomovitz, Eyster and Meek (22), and by Lewis, White and Meakins (23). The reference list is not exhaustive but the literature is fully reviewed in several of the references given. We have also briefly reviewed the literature on asphyxia in article III of this series (24).

The electrocardiographic method has been applied to the study of the changes in the mammalian heart in numerous studies from the laboratories of the University of Wisconsin by Eyster and Meek,

who used also the method of asphyxia to follow the point of origin of the pace-maker of the dying mammalian heart. In Lewis' laboratory in London, too, numerous electrocardiographic studies have tended to clarify our knowledge of the physiology both of the factors of intrinsic and extrinsic cardiac regulative control. Lewis and Mathison (18) showed that conduction and rhythm production are decreased even to the point of suspension when an animal with open chest is allowed to asphyxiate by stopping artificial respiration, and they have published electrocardiograms showing these points. Ganter and Zahn (14) and Meek and Eyster (21) found that if the sino-auricular node was cooled locally the pace-maker was driven to a lower point in the heart, i.e., the auriculo-ventricular node. This the latter proved by two leads taken directly from the exposed heart. Lewis, White and Meakins (23) showed that the displacement was by gradual steps in some animals, the cat, and by sudden shifts in others, the dog, as shown by shortening of the P-R interval. They observed that when the rhythm arises in the A-V node the conduction may be retrograde, as indicated by the R-P interval, a new point in mammalian heart physiology. Further asphyxiation suppressed the retrograde conduction and all evidence of auricular contractions disappeared. We call attention to the experiment of Lewis, Meakins and White on the cat, figure 6, plate 2, with the following legend: "After establishing A-V rhythm by applying cold continuously, a cat was asphyxiated; by the 145th second of asphyxia the heart passed through several stages of partial reversed block and finally the auricular contractions had vanished. The curve commences at this state and shows the recovery of the S-A node soon after the withdrawal of cold from it. The ventricular rate is practically unaltered and complete heart-block is evidenced by the dissociation of auricular and ventricular rhythms." This figure is quoted as direct experimental proof of asphyxial suppression of auricular contractions in the mammalian heart.

In our previous papers we have shown that in men during extreme oxygen-want very marked changes may occur in the mechanism of the human heart. These critical changes for the most part did not appear until the stage of oxygen-want in which the oxygen is insufficient to maintain the nervous system in conscious activity. In other words, the more profound changes during low oxygen are imminent at the approach of unconsciousness, and of skeletal muscular collapse, though cardiac slowing and disturbance of the normal mechanism follow these events in sequence. We have published examples in which two of the chief

irregularities of the human heart are loss of auricular contraction as evidenced by disappearance of the P wave, and loss of internodal conduction as indicated by dissociation. In the present paper we give in detail the reactions of an extreme case of this type, a case somewhat different but crucial as regards the nature and sequence of the local cardiac changes which we have followed without interruption.

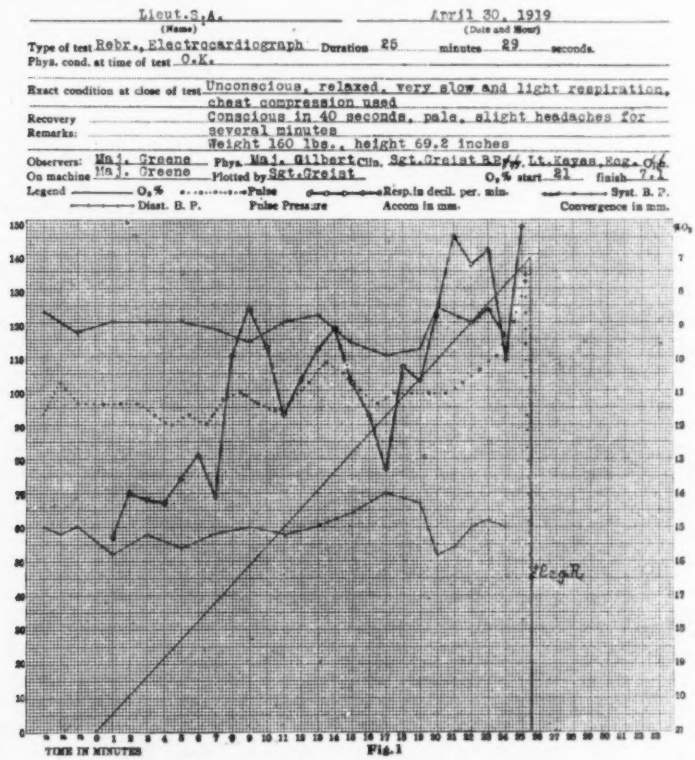
Lieut. S. A.
(Name)
April 30, 1919
(Date and Hour)
Type of test Rebr., Electrocardiograph Duration 25 minutes 29 seconds.
Phys. cond. at time of test O.K.
Exact condition at close of test Unconscious, relaxed, very slow and light respiration, chest compression used
Recovery Remarks: Conscious in 40 seconds, pale, slight headaches for several minutes
Weight 160 lbs., height 69.2 inches
Observers: Maj. Greene Phys. Maj. Gilbert Obs. Sgt. Greist R.B. Lt. Keyes, Eng. Off.
On machine Maj. Greene Plotted by Sgt. Greist O2% start 21 finish 7.4
Legend O2% Pulse Resp. in decil. per. min. Syst. B. P.
Diast. B. P. Pulse Pressure Accom in mm. Convergence in mm.
Neg. R.
TIME IN MINUTES

Fig. 1

Fig. 1. The clinical chart of Lieut. S. A. shows the heart rate, dotted line; systolic blood pressure, the top light line; diastolic blood pressure, the bottom line; respiratory minute-volumes, heavy line. The heart rates are taken by 20-second counts at the wrist during the first 20 minutes, and from the electrocardiogram from the 20th minute to the end of the record. The blood pressures are measured by the Rogers sphygmomanometer. The deciliters of air breathed per minute were read off the Larsen recorder. The blood pressure, heart rate and decileters of air are all shown by the legend to the left; oxygen percentages are indicated to the right.

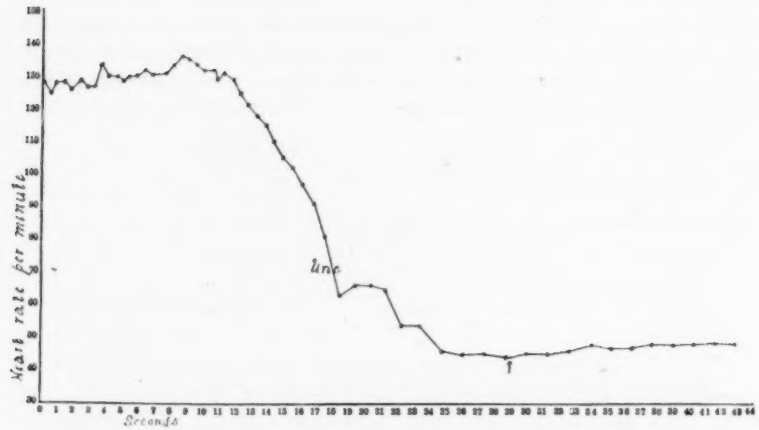

Fig. 2. The heart rate per minute of Lieut. S. A. during the post-crisis stage of oxygen-want, calculated beat by beat beginning with the 26th minute. *Unc*, became unconscious at about this point; *off*, removed from the test.

TABLE 1

Showing the variation in the pulse and in the electrocardiogram at intervals through the rebreather test. Time in seconds. Amplitude of the deflection in millimeters, equivalent to 10^{-4} millivolts. Lieut. S. A. April 30, 1919. Final oxygen 7.1 per cent. Time of run 25 minutes, 29 seconds. Equivalent altitude 28,000 feet

TRACE AND PULSE NUMBER	TIME IN MINUTES	OXYGEN IN PER CENT	DURATION IN SECONDS			AMPLITUDE IN MILLIMETERS				
			R-R	P-R	R-T	P	Q	R	S	T
1–10	Normal	21.0	0.656	0 136	0.320	0.8	None	14.0	1.0	2.4
2–4	5	18.2	0.648	0.140	0.328	1.0	None	13.5	1.2	2.3
3–2	10	15.5	0.624	0.140	0.292	0.9	None	15.0	1.6	1.8
4–1	15	12.7	0.640	0.152	0.312	0.9	None	13.0	1.4	1.8
5–20	20	10.0	0.584	0.144	0.280	1.0	None	12.0	1.5	1.6
6–122	22	9.0	0.700	0.152	0.296	1.0	None	11.5	1.0	1.8
7–237	24	7.9	0.568	0.136	0.280	0.9	None	12.0	1.4	1.0
8–275	25	7.3*	0.492	0.120	0.260	1.2	None	9.5	1.4	1.0

* Circulatory break at the end, see table 2. No recovery tracing secured.

TABLE 2

Variation in heart rate and in the electrocardiograms through the entire post-crisis stage of Lieut. S. A. The rates are computed on the basis of the length of the R–R intervals beginning at the crest of the maximum heart rate. The break occurred at 25 minutes, 10 seconds. The measurements of the P–R and R–T intervals are difficult and the factor of error is large. Lieut. S. A. April 30, 1919. Time of run 25 minutes, 29 seconds. Final oxygen 7.1 per cent—28,000 feet elevation.

TIME IN SECONDS BEGINNING AT 25 MINUTES	EQUIVALENT RATE FOR EACH CONSECUTIVE BEAT		ELECTROCARDIOGRAMS			REMARKS
	Pulse number	Rate	P-R interval	R-T interval	R amplitude	
10.00	1	132	0.13	0.26	11.5	
10.48	2	132	0.13	0.26	12.6	
10.90	3	129	0.13	0.26	12.4	
11.38	4	131	0.13	0.25	12.4	
11.84	5	129	0.13	0.27	12.6	
12.32	6	125	0.13	0.28	12.6	
12.80	7	121	0.13	0.29	13.0	
13.30	8	118	0.13	0.30	13.0	
13.32	9	116	0.14	0.31	12.4	
14.36	10	110	0.13	0.29	13.8	
14.96	11	105	0.12	0.30	14.0	
15.54	12	102	0.13	0.32	14.5	Muscular tremors severe during four beats
16.12	13	97	0.14	—	14.0	
16.80	14	91	0.13	0.33	13.4	
17.54	15	81	0.12	0.33	13.4	
18.48	16	63	0.112	0.33	13.0	P inverted
19.36	17	66	0.098	0.31	13.6	P inverted
20.28	18	66	0.094	0.30	13.0	P inverted
21.18	19	65	0.10	0.30	14.6	P inverted
22.30	20	54	0.10	0.34	14.0	P inverted
23.40	21	54	0.10	0.30	16.0	P inverted
24.68	22	46	0.10	0.31	16.0	P inverted
26.04	23	45	0.17	0.35	22.6	R–P or reversed conduction the P still inverted
27.36	24	45	0.21	0.33	22.3	
28.72	25	44	0.23	0.34	21.5	"Off" here
30.04	26	45	None	?	18.4	No P waves during the 10 recorded beats of this stage
31.26	27	45	None	?	16.5	
32.68	28	46	None	?	19.0	
34.00	29	48	None	?	18.0	
35.28	30	47	None	?	19.4	
36.58	31	47	None	?	18.0	
37.82	32	48	None	?	16.5	

Lieut. S. A. was carried to the stage of unconsciousness in an altitude test by the rebreather method, the procedure being the same as used in our previous research. Electrocardiograms were obtained at 5 minute intervals to 20 minutes, then a continuous electrocardiogram was recorded for the last 6 minutes and to the close of the test. The graph representing clinical progress of the entire test is shown in figure 1. The general electrocardiographic changes throughout the test are given in table 1. The heart rates calculated on the basis of the time of the successive cycles from a moment before the maxium heart rate through the terminal fall in rate to the end of the test are shown in figure 2. The electrocardiographic data for the critical post-crisis period is presented in table 2. The electrocardiograms representing the successive stages of the test are reproduced in plate 1, figures 1 to 8.

The general changes during the development of low oxygen are not essentially different from the types previously described. Lieut. S. A. follows the rule during the pre-crisis stage, both in the clinical cardio-vascular responses and in the changes shown by the electrocardiograms. The heart accelerated to 136 at the crisis, but with considerable variation in time of cycles between the 12th and 17th minutes. The systolic pressure fell during the 13th to 18th minutes, which, taken with the rise in diastolic pressure, the change in heart rate and the fall in respiratory volume, indicates a failure to adequately respond to the strain at this period. He rallied and continued to compensate until the 23rd minute and became unconscious in the 25th minute. These irregularities of compensation characterize nervousness during the test rather than weakness under the test. However, the test was made to the extreme limits and thus revealed vital and illuminating post-crisis changes in the heart.

Unconsciousness supervened at the point marked *Unc* in the electrocardiographic record, figure 8. He was continued in the test until his muscles began to relax, i.e., 10 seconds after the evidence of unconsciousness, and was then rapidly removed from the rebreather. Skeletal muscle relaxation became complete during removal of the mouth-

Plate I. The electrocardiogram of Lieut. S. A.; figure 1, normal; figure 2, after 5 minutes; figure 3, 10 minutes; figure 4, 15 minutes; figure 5, 20 minutes; figure 6, 22 minutes; figure 7, 24 minutes; figure 8, begins at 26 minutes and 10 seconds; figure 9, continuation of figure 8. The four shadows on figure 8 and the word *off* mark the point when Lieut. A. was taken off the test. The changes in heart rate in figures 8 and 9 are shown graphically in text figure 2. Time in fifth seconds. The R deflections of the original record have been strengthened by the engraver in reproducing the plate.

Fig. 1
Normal, pure air

Fig. 2
18.2 oxygen

Fig. 3
15.5 oxygen

Fig. 4
12.7 oxygen

Fig. 5
10.0 oxygen

Fig. 6
8.9 oxygen

Fig. 7
7.8 oxygen

Fig. 8. 7.2 oxygen

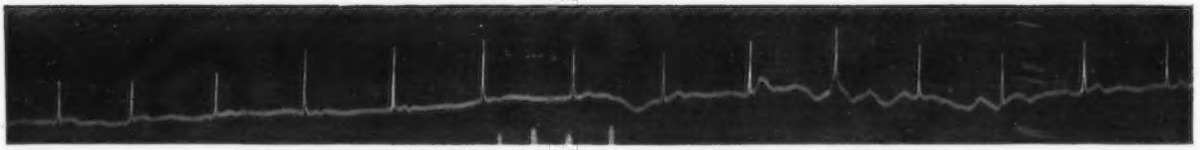

Fig. 9. Continuation of figure 8

piece, and relaxation continued to the end of the cardiographic record. His respirations at this time were very shallow and faint. Artificial respiration by compression of the thorax was produced at this point. Unfortunately at this critical time the electrocardiographic apparatus became disconnected so that the transitional stages toward cardiac recovery were not recorded. He remained unconscious about 40 seconds, then quickly and suddenly regained consciousness and muscular control. He was a little pale, was not nauseated, suffered some slight headache for several minutes, but otherwise showed no deleterious after-effects from the experience.

Both the clinical determinations and the heart rates obtained from the electrocardiograms show early progressive acceleration of the heart. This reaction is usually given by a normal compensator during the early and pre-crisis stages of the altitude test. The heart rate augmented from the rather high initial rate of 90 to a maximum of 136 per minute at the crisis at the beginning of the 25th minute. At this time the rate began to decrease, at first slowly through 6 or 7 beats, then very rapidly, until the low rate of 44 per minute was reached when the test was terminated. The beats remained at the slow rate for the remaining 10 seconds recorded.

The electrocardiogram taken continuously from the 20th minute, therefore including the time from the moment of maximum heart rate through the entire terminal or post-crisis period, shows in continuous panorama the facts on which we base the interpretation of the extreme effects of low oxygen on the behavior of the normal human heart. We emphasize above all the evidence that oxygen deficiency does not become vital to the heart itself until late, certainly not before the onset of unconsciousness. But when the crisis is reached the post-crisis changes occur rapidly, indeed in a few seconds.

The graph, figure 2, and the electrocardiogram,figures 8 and 9 of plate I, show that during 20 consecutive beats the rate dropped from 136 to 44 per minute. The rate was 100 at the beginning of a group of 4 contractions complicated in the electrocardiographic record by skeletal muscular tremors. Unconsciousness occurred during this period, according to the clinical evidence on which we base judgment. Lieut. S. A. did not immediately lose reflex control of his muscles, and still held the mouthpiece safely for a few seconds longer. The rate was 81 at the inversion of the P and the onset of unconsciousness and 66 at its consummation.

An inverted P wave appears during the last heart beat of the group in which skeletal muscular contractions occurred. This beat is coinci-

dent with a decided slowing in the rate, from 102 just preceding the unconscious stage to 64 during this beat. There is also a sudden reduction in the P-R interval showing that the time of conduction from the new source of the beat to the ventricular tissue is reduced, from 0.127 to 0.098 second (see table 2). Inversion of the P wave and shortening of the P-R interval are interpreted as signifying origin of the rhythm lower down in the system, i.e., the S-A node, or at least as low as the coronary sinus portion of the A-V node, as indicated in certain displacements observed by Ganton and Zahn, and by Meek and Eyster. The inverted P exists through seven successive contractions though the third contraction does not show the phenomenon clearly. In these seven beats the P wave precedes the R by a very uniform but shortened time interval.

On the third beat before the close of the test the P wave suddenly shifts to a post R position with a relatively long R-P interval. The last beat of the three in which this condition exists occurs at the moment of taking "off." Each successive R-P interval is longer, 0.17, 0.21 and 0.28 second, signifying the progressive and rapid loss of reverse conduction. This group of contractions indicates the shift of the rhythmic center to a still lower or third point of origin, presumably low in the A-V node. The sequence is reversed and conduction is back to the auricle. At this moment the rate is at its slowest, i.e., 44 to 45 per minute, where it remains with little variation during the last 10 beats recorded.

Augmentation in the amplitude of the R wave takes place at the time when the P shifts to the post R position. We offer no obvious explanation for this fact other than that the ventricle beats first in sequence, i.e., is the primary activity. During the last 10 beats the amplitude of the R varies little or none from beat to beat. The irregularity of the record from extrinsic currents confuses the R-S-T amplitudes to a degree.

The steps in the transition of the P outlined above indicate the suppression of the successive pace-making foci. The normal S-A node first succumbs during asphyxiation. The first ectopic rhythmic focus next ceases to function. There is finally left a rhythmic center well down in the conducting system adequate to maintain rhythm. It is true the rhythm is at a greatly reduced rate although the reduction is not so great as that often observed in pathological heart block.

At the moment of closing the experiment the P wave disappeared entirely. It did not reappear during the ten ventricular complexes of the remainder of the record. This we interpret as suppression of func-

tion of the conducting tissue sufficient to block conduction from the lower rhythmic center back to the auricle, demonstrating for man the additional new point that anoxemia blocks retrograde conduction from the ventricle toward the auricle during A-V rhythm. This was first shown to be true during systemic asphyxiation by the method of stopping respiration in lower animals by Lewis, White and Meakins who of course were dealing with excess of carbon dioxide as well as lack of oxygen. All the remaining contractions are normal ventricular complexes of the type in which the beat arises in the conducting system rather than in the muscle. No ectopic beats occurred in this case.

There is only the merest suggestion of an increase in rhythm during the ten beats that occur without auricular beats, in fact the rate is slow and remarkably regular from the moment the first R-P interval occurs.

This record gives conclusive evidence from the human subject that the pace-making function in the heart is depressed and lost in the descending direction during anoxemia induced by the rebreather method. The evidence from mammalian experimental sources is confirmed for the human. The most sensitive parts of the conducting system are the S-A node and the internodal region. These are both rendered inactive by oxygen-want long before rhythm and conduction are lost in the A-V node and the peripheral parts of the system. We believe these changes are immediately due to vago-spasm. But whether one accepts the explanation of vagal stimulation or of direct asphyxial effects, it is obvious that when for any reason, either physiological or pathological, the S-A pace-making center ceases to function and the auricular or internodal paths cease to conduct, thus suppressing auricular contractions, then the basic rhythmic property of the A-V node still persists to control the contractions of the ventricle for a time until the crisis passes. This control proceeds from the A-V node over the ventricle, and the rate though slow is adequate for a circulation of considerable efficiency. These observations agree with the deductions made in our previous paper. They confirm for man the facts pointed out by Meek and Eyster (20) for the dog, i.e., that the heart is sensitive to extrinsic control in the descending direction and "that the specialized tissues of the heart exhibit from above downward progressively diminishing degrees of automaticity."

The case of Lieut. S.A. differs from the others reported by us in that the shift of the point of origin of the rhythm and the loss of internodal conduction is by relatively sudden steps, rather than by progressive displacement of the pace-maker and of conduction.

The facts observed in our case are clear-cut and definite and we recognize that the practical significance in aviation and in clinical medicine is definite and clear. The slowing of the rhythm, inversion of the sequence to ventricle—auricle beats, and finally the decrease and disappearance of auriculo-ventricular conduction are all changes perfectly characteristic of over-activity of the vagus center. This human case might be explained on the basis of Mathison's observations of mammalian asphyxial vago-spasm. Wilson has shown that the S-A node is particularly sensitive to vagal control in man both in the normal (26), and in the stimulative stage of the action of atropine (27). Vagus action not only changes auricular rate but lowers auricular intensity, as shown by decrease in amplitude of the P. Change in amplitude of the P was not observed in Lieut. S.A. The P was inverted—not the usual type of vagus effect. The ventricular rate is most constant. In view of the evidence of direct vagal inhibitory influence over the A-V nodal rhythm, the failure of further ventricular slowing during the extreme anoxemia needs explanation on the vago-spasm hypothesis. However, we believe that the vagus stimulation hypothesis offers the most convincing explanation and is confirmed by this human case.

In the meantime we have in progress comparative experiments on mammals based on the rebreather-electrocardiographic methods which we hope will throw further light on the nature of the final post-crisis reactions of progressive oxygen-want as observed in man.

In closing this paper we again emphasize the numerous parallels we have observed in the physiology of the normal nodal system of the human heart in comparison with the facts of cardiography established on experimental animals. We also emphasize the correspondence as between simple anoxemia and the symptom complex of asphyxial cessation of breathing when excess of carbon dioxide is added to anoxemia.

SUMMARY

An additional and extreme case of oxygen deficiency on the normal human subject showing changes in the heart during a rebreather test is presented with continuous electrocardiograms through the crisis and post-crisis periods. The data show:

1. That reflex muscular control in the human may persist 6 to 8 seconds after loss of consciousness from anoxemia.

2. That sino-auricular rhythm is lost by steps first to a lower point in the sino-auricular system, second to a point nearer the base of the ventricle, presumably the auriculo-ventricular node.

3. That internodal conduction is finally lost a brief stage of reversed conduction terminating in lengthening R-P intervals precedes total loss of conduction.

4. That the ventricular rhythm is very persistent and unexpectedly regular during the late post-crisis stage. In this case the equivalent rates are from 63 to 44 increasing to 48 per minute in 10 seconds after removal of the mouth piece.

5. That in man lack of oxygen induces a series of changes in cardiac rhythm, in conduction and in suppression of auricular contractions quite parallel to similar phenomena established in experimental animals under general asphyxiation.

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OSCILLATIONS IN DIAPHRAGM MUSCLE

L. B. NICE AND ALMA J. NEILL

From the Laboratory of Physiology in the University of Oklahoma

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That oscillations appear in diaphragm muscle under various conditions has long been known. Mosso observed them in dogs and rabbits in normal sleep and under anesthesia (1). We have observed these oscillations in urethanized dogs, cats and rabbits and in decerebrate cats and rabbits (2). The reason for their appearance does not seem to have attracted much attention. In searching through the literature we have been unable to find data to locate their exact cause. There seems, however, to be a general consensus of opinion that they are due to central origin (3). In an attempt to find out whether these oscillations may not be due in part to peripheral origin, the following experiments were undertaken.

METHODS

The animals used in this investigation were pithed cats and dogs which were previously anesthetised with ether or with urethane (2 grams per kilo of body weight) by stomach. At times ether was also administered to the urethanized animals to hasten the anesthesia before operating. An animal was fastened back downward to an animal holder, a cannula inserted into a femoral artery, and a mercury manometer attached for recording the blood pressure which was used as an indicator for the general condition of the preparation and for comparison with contractions of the diaphragm muscle.

The abdominal cavity was opened by a median incision and an S-shaped hook attached to the diaphragm about midway between the central tendon and the lateral chest wall as previously used by Nice and his co-workers (4). From the S-shaped hook a thread was passed over a pulley to a light writing lever which recorded the contractions of the diaphragm on a revolving drum. In some of the experiments a plethysmograph record was also made of the chest wall but no change in the record took place so it was omitted later.

In the earlier experiments the urethanized animals were permitted to write simultaneous records of their blood pressure and movements of the diaphragm until oscillatory waves appeared in the latter; but soon this was found unnecessary so the stimuli were applied at once. A tracheal cannula for artificial respiration was inserted, both phrenic nerves severed in the neck, and a Harvard shielded electrode placed on the peripheral end of a transected phrenic on the same side on which the S-shaped hook had previously been attached to the diaphragm. Both carotid arteries were tied off and the cord transected through the foramen magnum and the brain pithed. Artificial respiration was applied for from 2 to 5 minutes and then the peripheral end of a cut phrenic nerve was stimulated with a series of break-induction shocks. Artificial respiration was again applied and a new series of break induction shocks sent into the nerve and so on. The temperature of the animal was maintained by an electric heater.

The stimulating current for the phrenic nerve. The stimuli used for the peripheral end of the phrenic nerve were a series of break induction shocks obtained from a vulcanite key which is a modification of the original one described by Martin (5). The key was operated by a motor running at a uniform rate. The number of stimuli used varied from 120 to 188 per minute, however, 148 was the usual number employed, yet the other figures seemed equally satisfactory. The strength of the stimulus was the same throughout a single experiment.

RESULTS

Types of oscillations. In taking up the results of this work it should be stated that oscillations appeared most prominently in vigorous, well-nourished animals while they failed to appear only in a few asthenic ones. Another fact that should be noted is that these oscillations may appear and disappear or take an entirely different form under the same strength of stimulus, and the amplitude of the curve may vary greatly.

In figure 1 the peripheral end of the left phrenic of a pithed dog was stimulated 148 times per minute. It is seen that the oscillations show great variation. At *B* the rate of speed of the drum was increased to get the individual variations in the single contractions of the muscle. Oscillations similar to those in the first part of the curve *A* reappear. Figure 2, which was taken on the same animal about 30 minutes later than figure 1, shows more marked oscillations.

Figure 3 was obtained from the right side of the diaphragm muscle in a decerebrate cat. In *A* the typical oscillations that appear are seen while *B* is a continuation of the stimulations in *A* after an intermission of 2 minutes during which time artificial respiration had been administered. Although the strength of stimulus and the rate of stimulation were the same as in *A*, the muscle curve in *B* shows no oscillations.

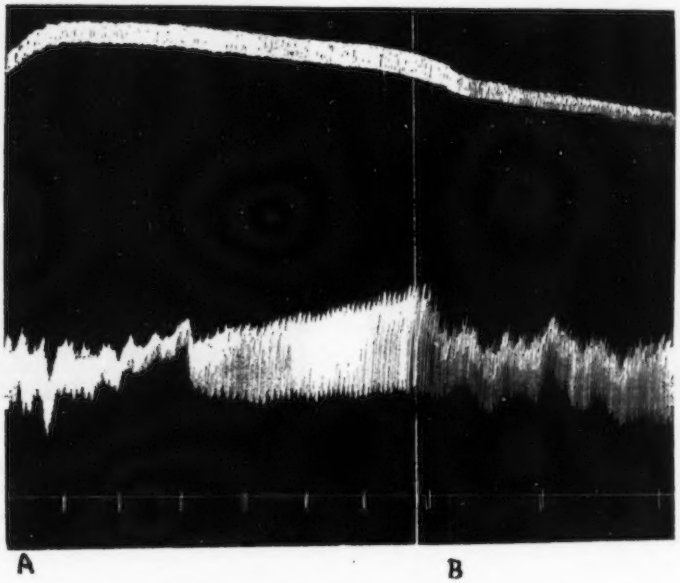

Fig. 1. Dog A. In this and all following records the upper curve indicates the blood pressure; the middle curve the contractions of the diaphragm; and the lower line the time in half-minutes. The left phrenic nerve was stimulated with break induction shocks at the rate of 148 per minute. In *B*, which is a continuation of *A*, the rate of speed of the drum was increased.

This is a common occurrence in these experiments. We have also observed that oscillations may be obtained on one half of the diaphragm and refuse to appear on the opposite side.

Relations of the oscillations to blood pressure. The blood pressure in pithed animals is known to be low. In figure 1 and figure 2 there are no changes in blood pressure from the level that can account for the oscil-

lations in the diaphragm muscle. In figure 3, *A*, there are some variations in blood pressure but not of sufficient size, it would seem, to account for the changes in the curve of the diaphragm muscle.

Fig. 2

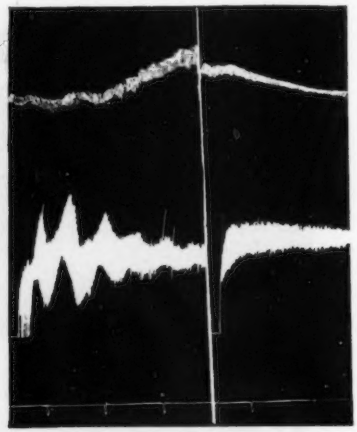

Fig. 3

Fig. 2 Dog A. This record was obtained on the same animal as figure 1 about 30 minutes later.

Fig. 3. Cat. Oscillations in the right half of the diaphragm Phrenic nerve stimulated 176 times per minute. *B* is a continuation of *A* after an intermission of 2 minutes.

DISCUSSION OF RESULTS

Diaphragm muscle is unlike some other striated muscles in that it is more resistant to fatigue, more resistant to death after excision from the body, and is less injured in inanition (5).

Relation of blood pressure. In pithed animals the blood pressure is low yet these oscillations appear on stimulation of the peripheral end of a cut phrenic nerve.

Cannon and Gruber (6) have shown that oscillatory waves appear in the tibialis anticus muscle of the cat in pithed animals and also in excised perfused muscle under rhythmic Faradic stimulation so that blood pressure seems not to be a factor in these cases.

Source of oscillations. Oscillations in diaphragm muscle are generally considered to be of central origin (7). Our results show that they appear when the nerves from the central nervous system are severed and the peripheral end of a phrenic is stimulated with break induction shocks.

Lee and his co-workers found "rhythmicity" appearing in isolated diaphragm muscle of the cat when it was stimulated directly at a uniform rate (8). The question arises as to whether this "rhythmicity" may not be a characteristic of the muscle itself that has given rise to the oscillations in our experiments with the muscle in situ.

Since the upper cord was pithed and both phrenic nerves transected, these oscillatory waves must be of peripheral origin and would seem to be due to changes in the irritability of the muscle itself.

SUMMARY

1. Oscillations in diaphragm muscle similar to those occurring in animals in normal sleep and under anesthesia and in decerebrate cats and rabbits may appear when the cord is pithed in the cervical region, the brain destroyed, both phrenic nerves transected and the peripheral end of one stimulated with break induction shocks.

2. These oscillations take different forms and may appear, disappear and re-appear under the same strength of stimulus.

3. There seems to be no relation between changes in blood pressure and the character of the oscillations in diaphragm muscle in pithed animals.

4. The evidence indicates that the oscillations in our experiments are due to changes in the irritability of the diaphragm muscle itself.

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